TAK-659 in Combination with NKTR-214 and anti-PD-1 Therapy Leads to Complete and Sustained Tumor Regression and Immune Memory In Pre-Clinical Syngeneic Models

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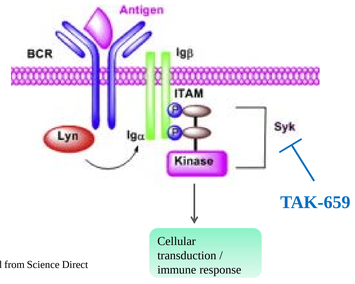
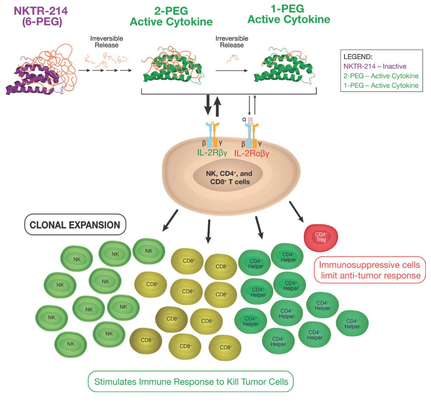
Introduction

- TAK-659 is a highly potent, reversible inhibitor of spleen tyrosine kinase (SYK) and fms related tyrosine kinase 3 (FLT3) that is being tested in combination with nivolumab in patients with advanced solid tumors (NCT02834247).
- NKTR-214, a CD-122-biased agonist that targets the IL-2 pathway, provides sustained signaling through the heterodimeric IL-2 receptor pathway (IL-2Rβɣ) to preferentially activate and expand NK and effector CD8+ T cells over T-regulatory cells in the tumor microenvironment, and is currently in multiple Phase I and II clinical trials in combination with checkpoint inhibitors (NCT02983045, NCT03138889).
- Treatment with TAK-659 in pre-clinical models resulted in a decrease in MDSCs and B220+ B-cells, while NKTR-214 monotherapy increases newly proliferative CD8+ T cells in tumors, increases cell surface PD-1 on immune cells and PD-L1 on tumor cells (Kannan, K. et al. European Journal of Cancer , Volume 69 , S92; http://www.nektar.com/application/files/7714/7887/7212/2016_SITC_NKTR-214-clinical_poster.pdf).
- Here we explored the pre-clinical combination of TAK-659 with NKTR-214 in the presence or absence of anti-PD-1 therapy in multiple syngeneic tumor models.

TAK-659 / NKTR-214 Mechanism of Action

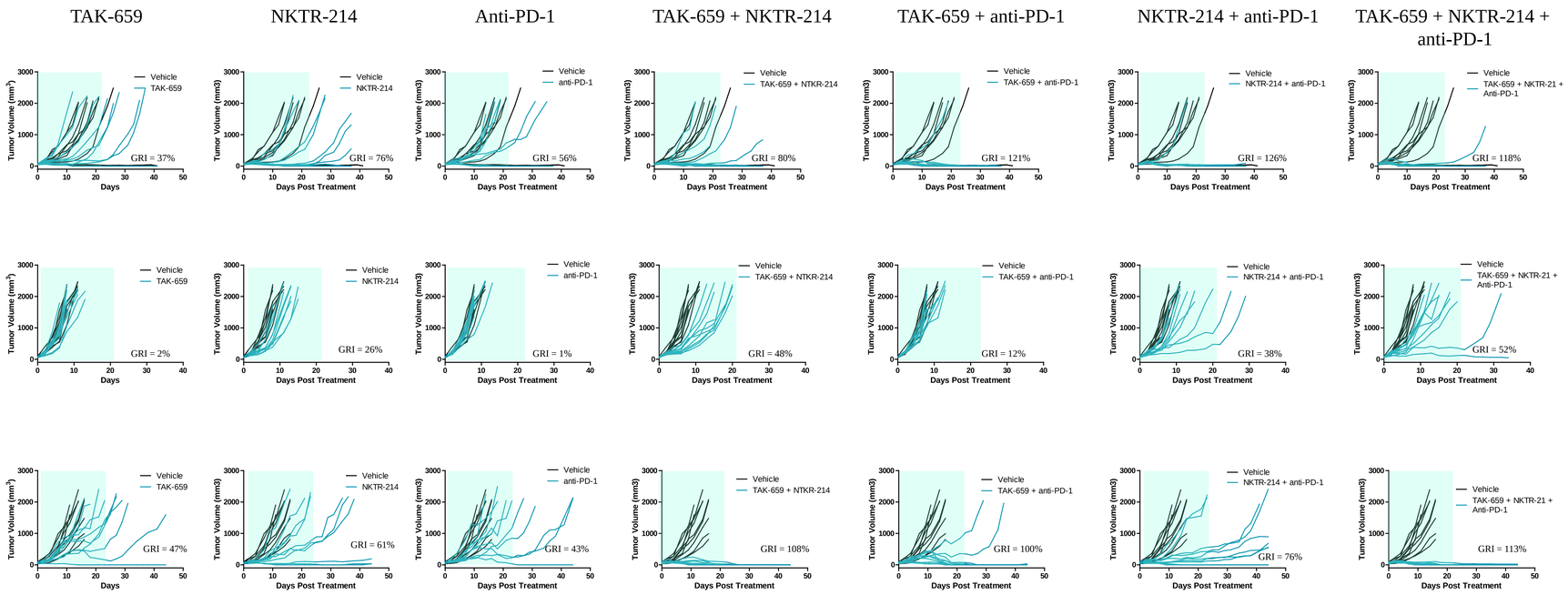


Modified from Science Direct

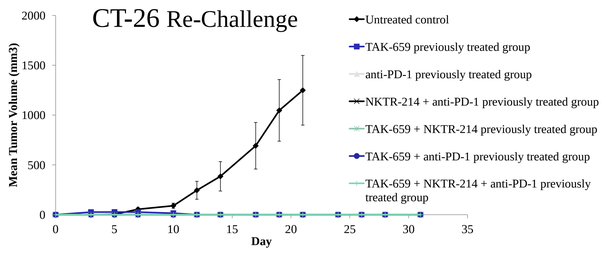


Antitumor Activity of TAK-659 in Combination with NKTR-214 and anti-PD-1 Therapy in Pre-Clinical Syngeneic Models *in Vivo*

A.



B.



A. BALB/c mice (A20, CT-26) or C57/BL6 mice (B16F10) bearing A20 syngeneic lymphoma, B16F10 syngeneic melanoma, or CT-26 syngeneic colon tumors (n=10/group) were treated with vehicle, TAK-659, NKTR-214, anti-PD-1 therapy, or in combination for 21 days. The details of the treatment regimen are shown below, and the shaded area of the plots represents the treatment period. Growth rate inhibition values (GRI) = 100% x (mean growth rate of vehicle– mean growth rate of treatment) / (mean growth rate of vehicle), were calculated on Day 21 of treatment. All animals were handled according to IACUC guidelines and removed from study when they reached the humane endpoint. All animals remaining on study were treated for 21 days.

B. Complete responders from the CT-26 study (animals with tumor volume = 0mm^3) were re-challenged with CT-26 tumor cells on the opposite flank along with a naïve cohort as a control on Day 45. 5 out of 5 untreated control mice formed tumors, whereas none of the previously treated mice formed tumors.

Treatment Schedule

Test Article	Dose	Route	Schedule
Vehicle 0.5% MC Nektar Buffer PBS	N/A	 PO IV IP	 QD Q9D BIW
TAK-659	60mg/kg	QD	PO
NKTR-214	0.8mg/kg	Q9D	IV
anti-PD-1	200ug/mouse	BIW	IP

BIW = twice weekly; IP = intraperitoneal(ly); IV = intravenous(ly); MC =methylcellulose; N/A = not applicable; PBS = phosphate buffered saline; PO = oral(ly); QD = once daily; Q9D = every nine days (one day dosing and 8 days off);

Summary

- TAK-659 in combination with NKTR-214 with or without anti-PD-1 therapy resulted in significant antitumor activity and durable complete tumor regressions in multiple models.
- In the CT-26 murine colon cancer model, the TAK-659 + NKTR-214 treatment group or the triple combination group with anti-PD-1 therapy resulted in 9 out of 10 mice having a maintained complete response (CR) 55 days post the end of treatment.
- Complete responders from the CT-26 study, left untreated and re-challenged with another inoculation of tumor cells on the opposite flank, did not form tumors, suggesting a potential immune memory in all treatment groups.
- TAK-659, NKTR-214, and anti-PD-1 therapy bring together complementary non-overlapping mechanisms that create a promising potential therapy, supporting the rationale for examining the clinical combination.