Evaluation of the Efficacy of a CD122-Biased Agonist for Treatment of Melanoma as a Monotherapy and in Combination with PD-1 Inhibition Using a Mechanistic Mathematical Model

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Introduction

- Melanoma is the fifth most common cancer in the United States
- The prognosis of patients with metastatic melanoma is poor, with a 5-year survival rate between 5-19%
- Despite recent advances in immunotherapeutic approaches, it has been challenging to predict which patients will respond to treatment
- There is a pressing need for new therapies which would show efficacy in a broad range of patients

Objectives

- Our primary objective was to evaluate the **efficacy** of a novel CD122 (IL-2 receptor β/γ)-biased agonist (NKTR-214) as a monotherapy and in combination with an anti-PD-1 mAb (nivolumab) using a Quantitative Systems Pharmacology (QSP) methodology
- Our secondary goals included evaluation of **dosing strategies**, identification of **responders vs. non-responders** characteristics**,** and assessment of **key biological pathways impacting outcomes**

Methods

The Melanoma Immuno-Oncology PhysioPD™ Platform represents key biological pathways involved in metastatic melanoma and responses to specific immunotherapies

- The Melanoma Immuno-Oncology PhysioPD Research Platform (Platform) is a mathematical representation of the physiology of a single metastatic melanoma tumor (Figure 2)
- The Platform represents the following biological functions:
  - Dynamics of tumor growth, tumor cell lifecycle
  - Immune cells (T cells, NK cells and APCs) recruitment, activation, proliferation, and functions
  - Production and downstream effects of key mediators involved in the pathophysiology of the disease and therapy response
  - IL-2 and PD-1 receptors and their interactions with ligands
  - Pharmacokinetics and pharmacodynamics (PK/PD) of aldesleukin (IL-2), nivolumab, and NKTR-214
  - Calculation of a clinical outcome:
    - Sum of longest diameters (SLD)
- Rosa's Model Qualification Method was used to ensure the model was fit-for-purpose (Figure 1)
- Virtual Patients (VPs) with variability in mechanistic pathways (e.g., PD-L1, IL-2 receptor expression, intra-tumoral leukocyte population, NKTR-214 penetration into the tumor, necrotic core size) and clinical responses to IL-2 and anti-PD-1 therapies were created
- The VPs were used for simulations to address the research objectives

Figure 1. Diagram of Rosa's Model Qualification Method[1] (MQM)

- Abbreviations: Nivo = nivolumab; alt=alternative cycles of nivolumab 360 mg and NKTR-214 0.006 mg/kg QW3; preload= 2 cycles of nivolumab 360 mg or NKTR-214 0.006 mg/kg followed by nivolumab 360 mg + NKTR-214 0.006 mg/kg QW3

The Platform Development

The Melanoma I-O PhysioPD Research Platform represents biological components involved in the pathogenesis of metastatic melanoma, mechanisms of immunotherapies, and clinical outcomes

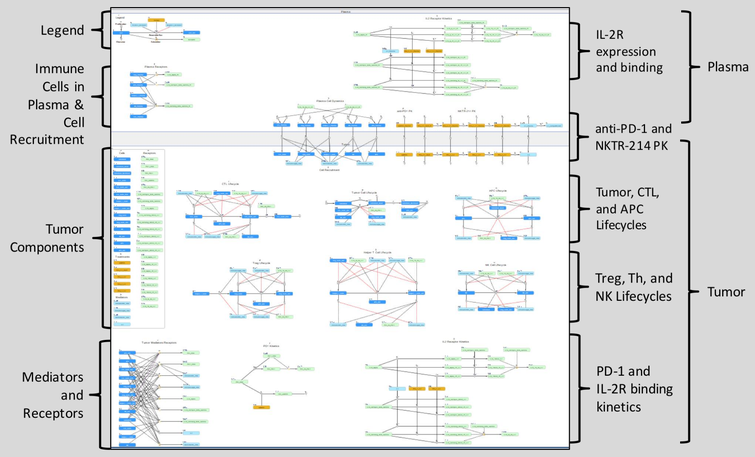

Figure 2. The Melanoma I-O PhysioPD Platform represents the pathophysiology of a **single melanoma metastatic tumor** (for details see Methods). Data and scientific knowledge from numerous sources are integrated into a single contextual framework. The Platform was developed using MathWorks® SimBiology software

The Platform Qualification

The Platform was qualified to match behaviors reported in the literature and proprietary data

- Qualification was based on a wide range of public and proprietary data, including tumor size, growth rate and composition, immune cell populations (tumor and blood), mediator production rates, receptor expression levels, turnover rates of cells and mediators, clinical, cellular and subcellular changes in response to treatments, and PKs for nivolumab, aldesleukin and NKTR-214
  - NKTR-214 PK was based on Charych et al. 2017 model adapted for humans [2]

Parameter (% of total tumor cells)	Post-treatment value (at 1-2 months)	
	Data	Simulation
CD45+ (Leukocytes)	25%	29%
CD3+ T cells	10%	8.2%
CD4+ T cells	3.3-4.5%	4%
CD8+ T cells	5-6.7%	4.2%
Tregs	0.5-0.8%	1%
CD8/Treg ratio	6.2-13.4	4.1
NK cells	1.25%	2%

Table 1. This example shows agreement between reported changes in immune cell population in the tumor following anti-PD-1 treatment (Ribas et al. 2016 [3] and Daud et al.2016 [4]) and simulated Platform results. Similar agreement was achieved for simulated aldesleukin and NKTR-214 treatments (not shown)

Results: Efficacy

Simulated NKTR-214 and nivolumab combination is strongly beneficial in a VP who does not respond to nivolumab monotherapy

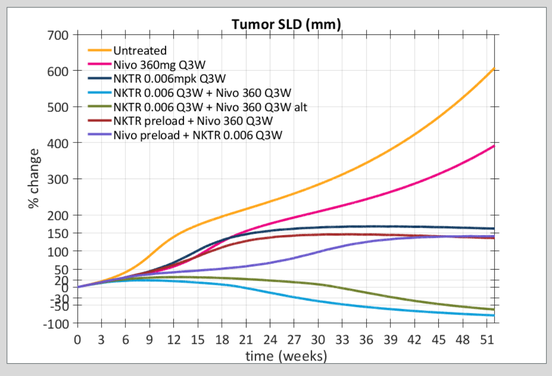

Figure 3. In silico research shows the increased efficacy of NKTR-214 and nivolumab combination in a VP not responding to either monotherapy.

See Methods for explanations of abbreviations and dosing details

Results: Dosing

Simultaneous combination dosing provided more benefit compared to alternate dosing

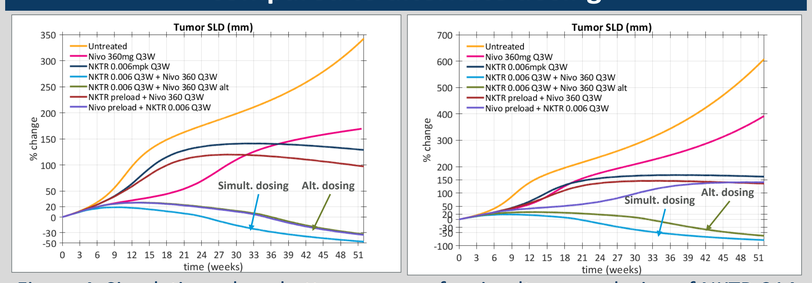

Figure 4. Simulations show better response for simultaneous dosing of NKTR-214 0.006 mg/kg Q3W + nivolumab 360 mg, compared to alternate dosing in VPs not responding to nivolumab. Examples show VPs with partial (left) and complete (right) response to combination dosing. See Methods for explanations of abbreviations and dosing details

Results: Biomarkers

Intra-tumor CTL:Treg ratio was identified as a candidate biomarker of therapy outcomes

- Under current Platform assumptions, to achieve partial response, the CTL:Treg ratio in the tumor has to be ≥ 2.5 (Figure 5, left panel, black line)

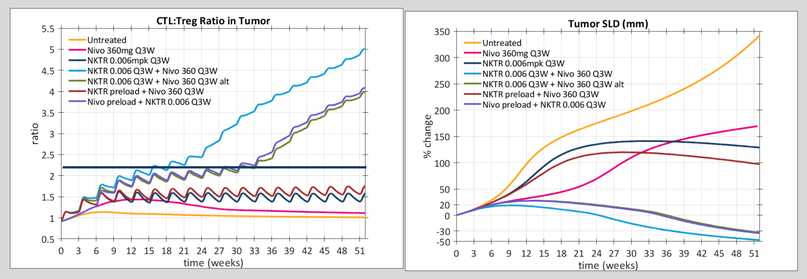

Figure 5. CTL:Treg ratio correlates with therapy response in a VP with progressive disease in response to nivolumab and NKTR-214 monotherapy. Combination therapies that result in a partial or a complete response (right) have a high CTL:Treg ratio (left). See Methods for explanations of abbreviations and dosing details

Results: Mechanisms

Research in the Platform indicated potential key drivers of combination therapy response

- Sensitivity analysis identified the following key mechanisms that impacted the therapy outcome:
  - PD-1 inhibition of CTL/NK effector function
  - Immunostimulatory and immunosuppressive mediator regulation
  - Necrotic core size and clearance rate
  - Levels of PD-L1 expression
  - Baseline tumor CTL:Treg ratio
  - NKTR-214 penetration into the tumor
- VPs with high tumor PD-L1 expression were more progressive at baseline and most of them responded well to nivolumab monotherapy due to a high number of exhausted CTL cells present in the tumor, which can be rapidly reactivated by anti-PD-1 therapy
- VPs with high CTL:Treg ratio benefited from adding NKTR-214 to nivolumab monotherapy

Conclusions

- Exploratory analyses using mechanistic model suggests the novel drug NKTR-214 combined with nivolumab shows superior efficacy compared to nivolumab alone in nivolumab non-responder VPs
- Simultaneous dosing of NKTR-214/nivolumab is likely more efficacious than sequential alternate dosing or preloading with either drug
- Intra-tumor CTL:Treg ratio can be used as a potential marker of combination therapy response
- Key mechanistic drivers of combination therapy response have been identified (see Mechanisms)

References

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