Preclinical development of NI-3201, a PD-L1xCD28 bispecific antibody mediating CD28 costimulation upon PD-L1 blockade

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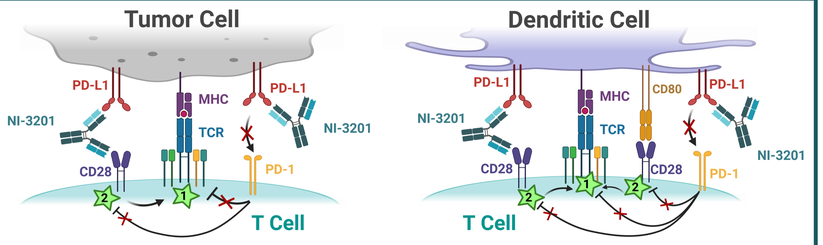
Abstract 5293

Combining PD-L1 blockade with CD28 costimulation



1. **Blocks PD-L1|PD-1** interaction to remove the brake on CD28 signaling
2. **Provides** T cell activation **signal 2** when bridging PD-L1+ cells and T cells

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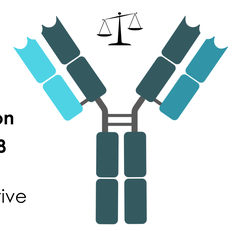
PD-L1-dependent delivery of Signal 2

anti-PD-L1 arm

- Binds to **PD-L1 positive tumor and APC cells**
- **Blocks PD-L1|PD-1 interaction**
- Allows the **clustering of CD28** at the surface of T cells
- Is Cyno & mouse cross-reactive



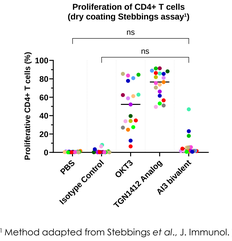
anti-CD28 arm

- Is an antagonist arm per se
- Turns into an **agonist arm** delivering T cell Signal 2 **after co-engaging PD-L1**
- Is cyno cross-reactive

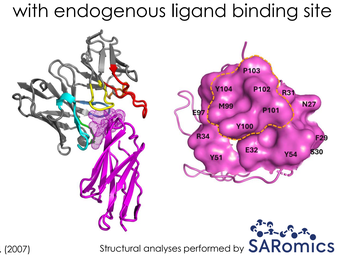
- Designed with unbalanced arm affinity and silenced Fc part
- Truly native human bispecific IgGs built on the κλ body platform (two identical heavy chain naturally paired to one kappa and one lambda light chain)
- Light chain CDRs drive specific binding to selected antigen

Anti-CD28 arm of NI-3201 is not superagonist

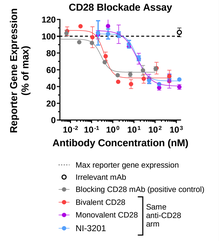
1. No superagonism



2. Apical binding epitope overlapping with endogenous ligand binding site



3. Antagonistic Activity

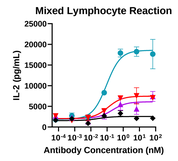


[1] Method adapted from Stebbings *et al.*, J. Immunol. (2007)

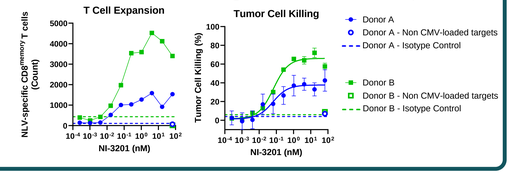
Structural analyses performed by SAROmics

NI-3201 boosts T cell activation through delivery of Signal 2

1. Enhanced APC activation in Mixed Lymphocytes Reaction



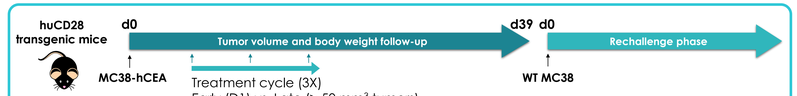
2. Expansion of NLV-specific CD8^{memory} T cells and tumor cell killing in CMV-recall assay

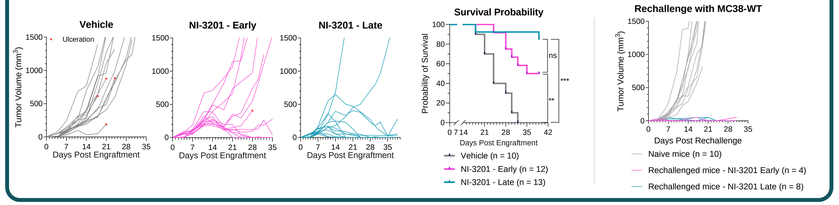


NI-3201 single-agent anti-tumor activity *in vivo*

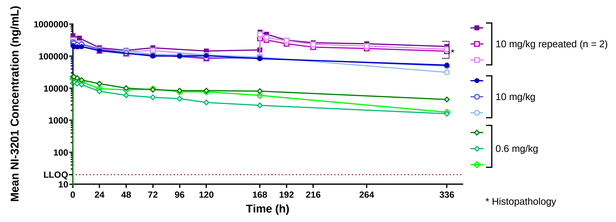
1. NI-3201 controls established MC38-hCEA tumors in immunocompetent huCD28 mice

2. NI-3201 induces immunological memory against WT MC38





Well-tolerated with favorable PK in cynomolgus monkeys



Histopathology:
No treatment-related macroscopic or microscopic changes noted in the examined organs after repeated intravenous administration of NI-3201

- Macroscopic examination on most organs
- Histological examination performed on brain, heart, kidneys, liver, lungs, mandibular lymph nodes, mesenteric lymph nodes and spleen

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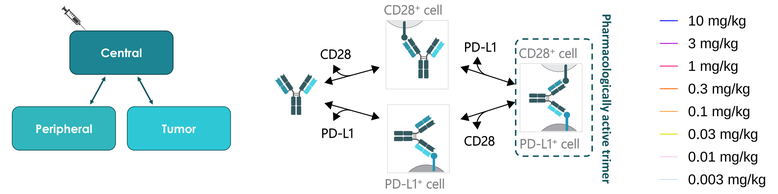
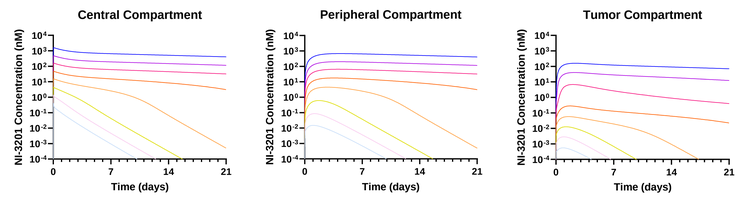
Modelling predicts achievable therapeutic exposures in patients

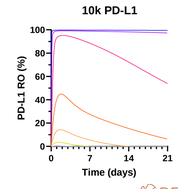
Human 3-compartment, semi-mechanistic PK/PD model



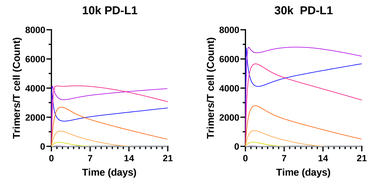
Predicted exposure in patients



Predicted PD-L1 RO



Predicted trimer formation



QSP modeling performed by RESIDUAL DYNAMICS

Status and next steps

- Favorable scientific advice received from EU agencies validating preclinical package and clinical plans
- Clinical GMP production in progress
- Phase I clinical trial initiation expected H1, 2025
- Several other TAAxCD28 κλ bodies under development: