NI-3201, a PD-L1xCD28 bispecific antibody for immune checkpoint-dependent CD28 costimulation

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NI-3201 combines PD-L1 blockade with CD28 co-stimulation
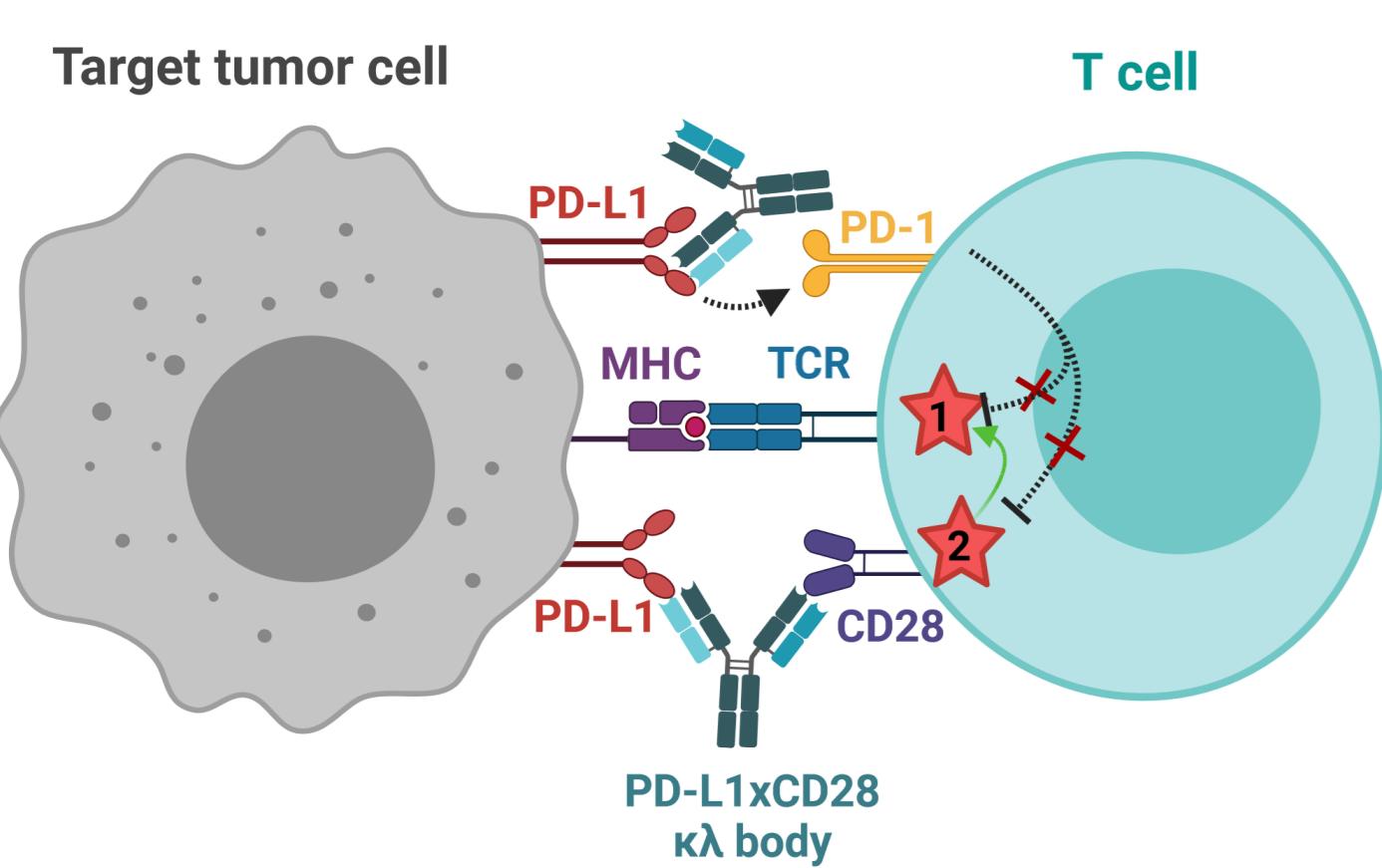
1. Blocks PD-L1|PD-1 interaction to remove the brake on CD28 signaling
2. Provides T cell activation **signal 2** when bridging PD-L1^{+} cells and T cells

## The κλ body platform – Truly native bispecific IgGs
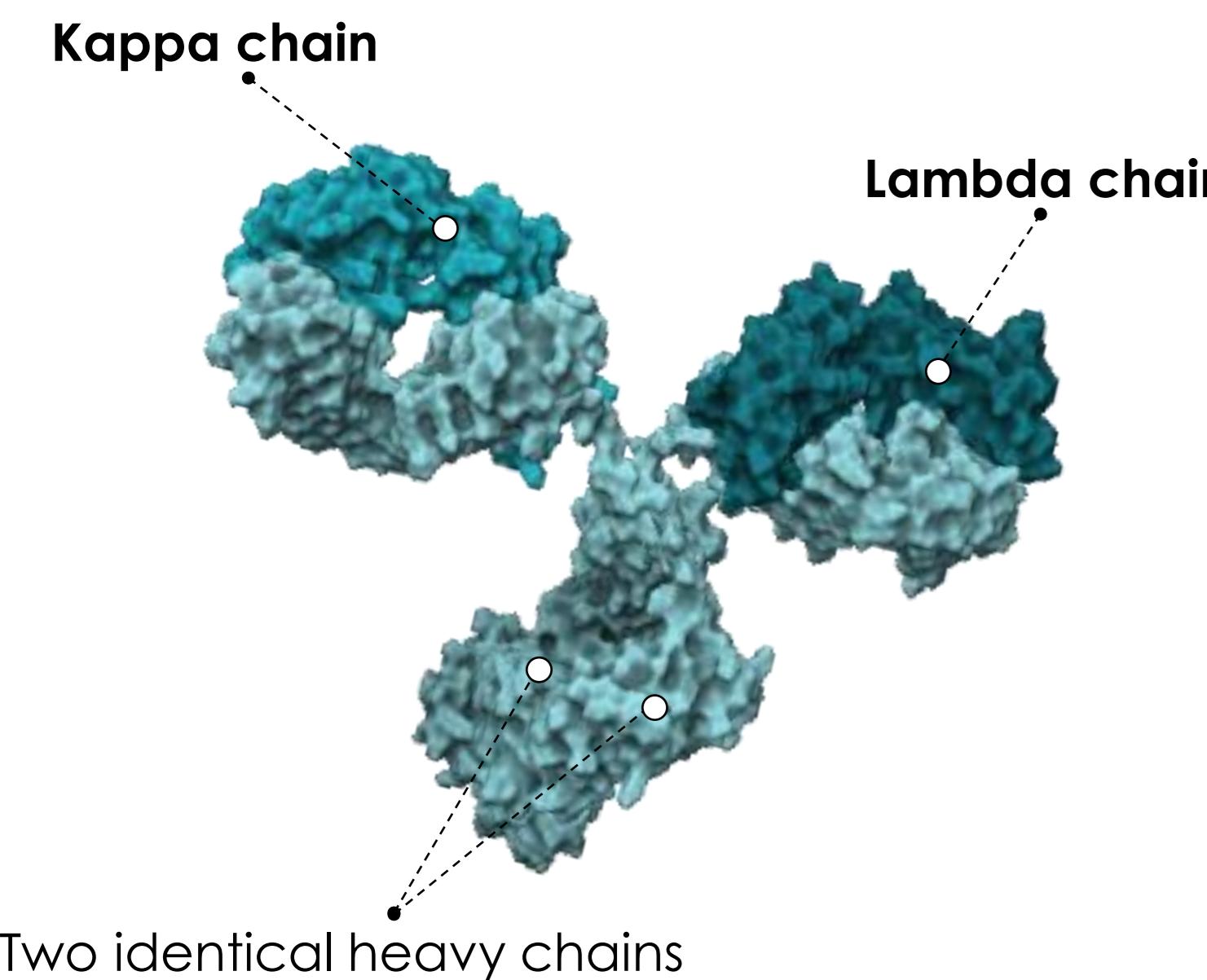
- Unmodified native human antibody sequence and structure
- Indistinguishable from natural human IgGs
- Light chain CDRs drive specific binding to selected antigen
- Favorable CMC properties
  - Platform purification process
  - Multiple GMP runs performed
- 2 clinical stage programs and several other κλ bodies in development, including various partnered programs

PD-L1-dependent delivery of Signal 2

Unbalanced affinity
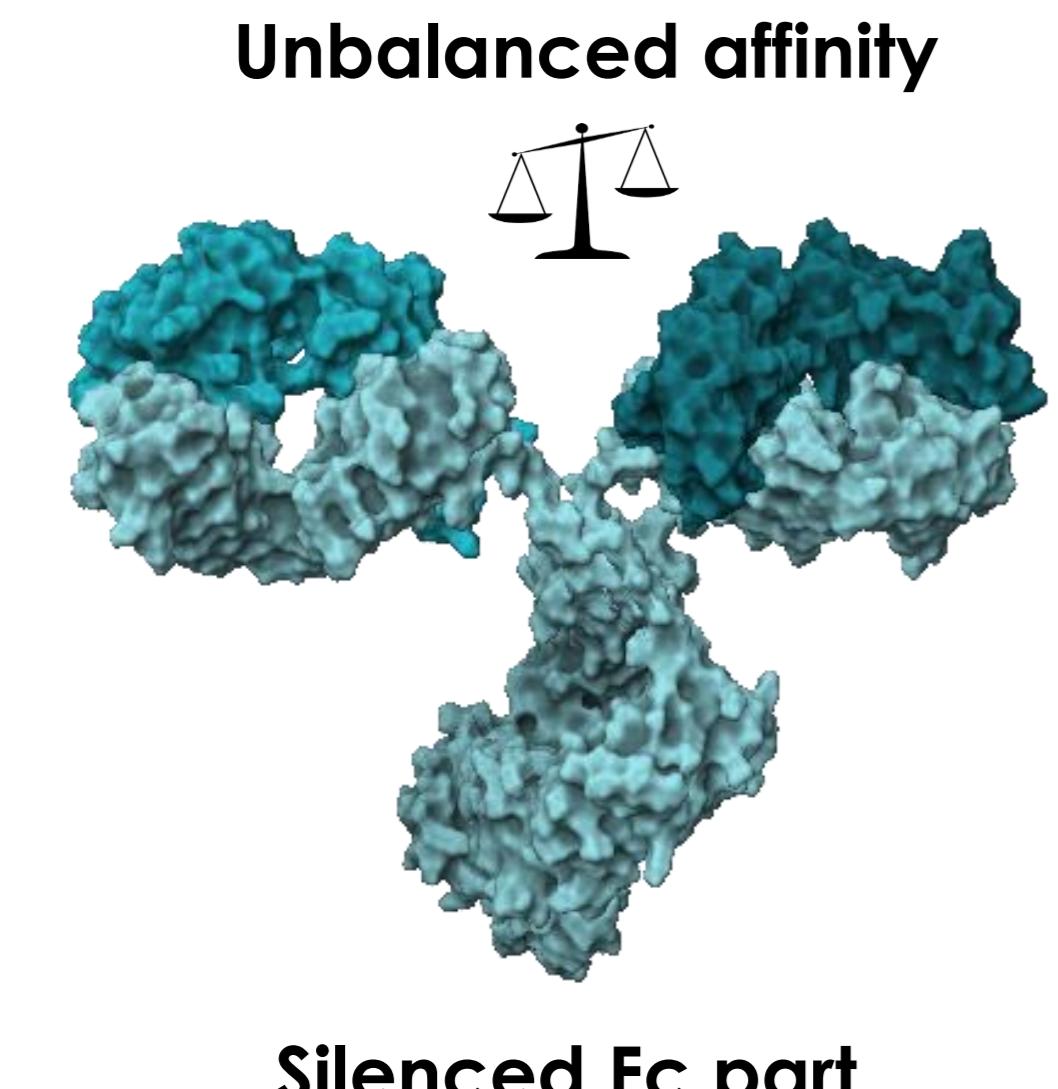
anti-PD-L1 arm
- Blocks PD-L1|PD-1 interaction
- Clusters CD28 on T cells
- Cyno & mouse cross-reactive

anti-CD28 arm
- Agonist arm: PD-L1 dependent CD28 activation
- Cyno cross-reactive

Silenced Fc part

Anti-CD28 arm of NI-3201 is not superagonist

1. Sensitive in vitro cytokine release assays
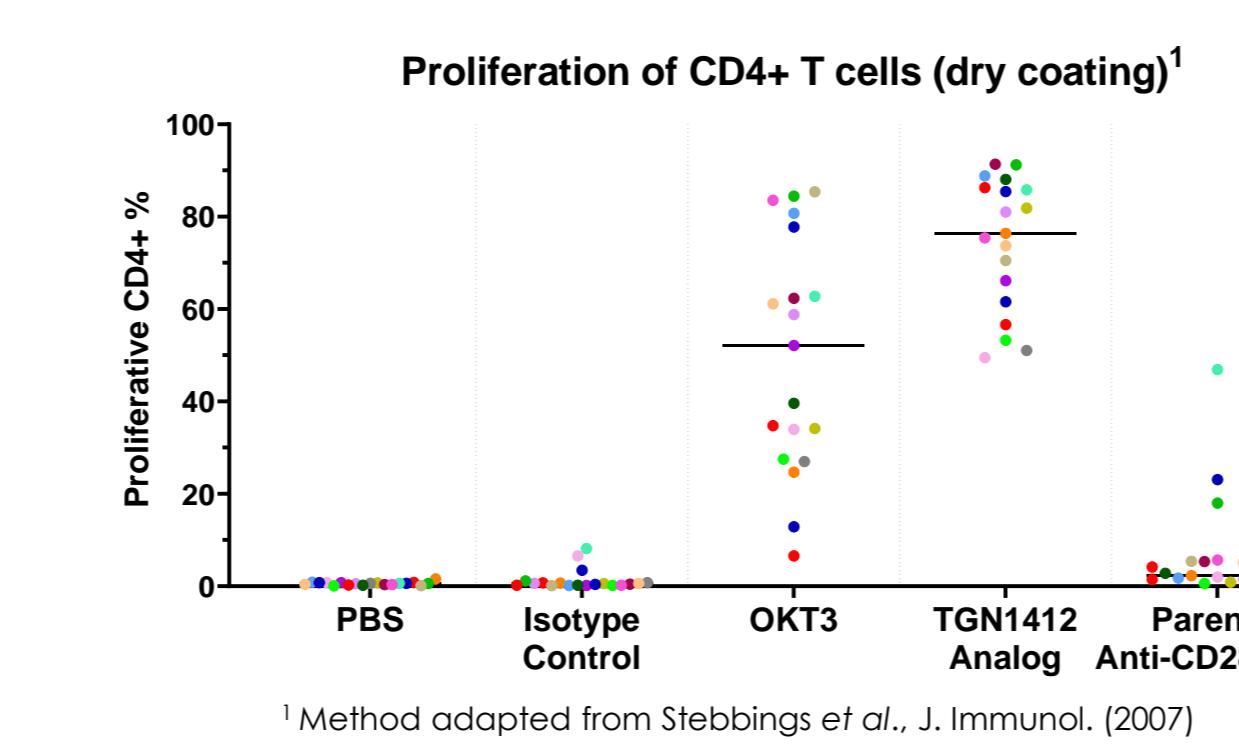
[1] Method adapted from Stebbings et al., J. Immunol. (2007)
[2] Method adapted from Römer et al., Blood (2011)
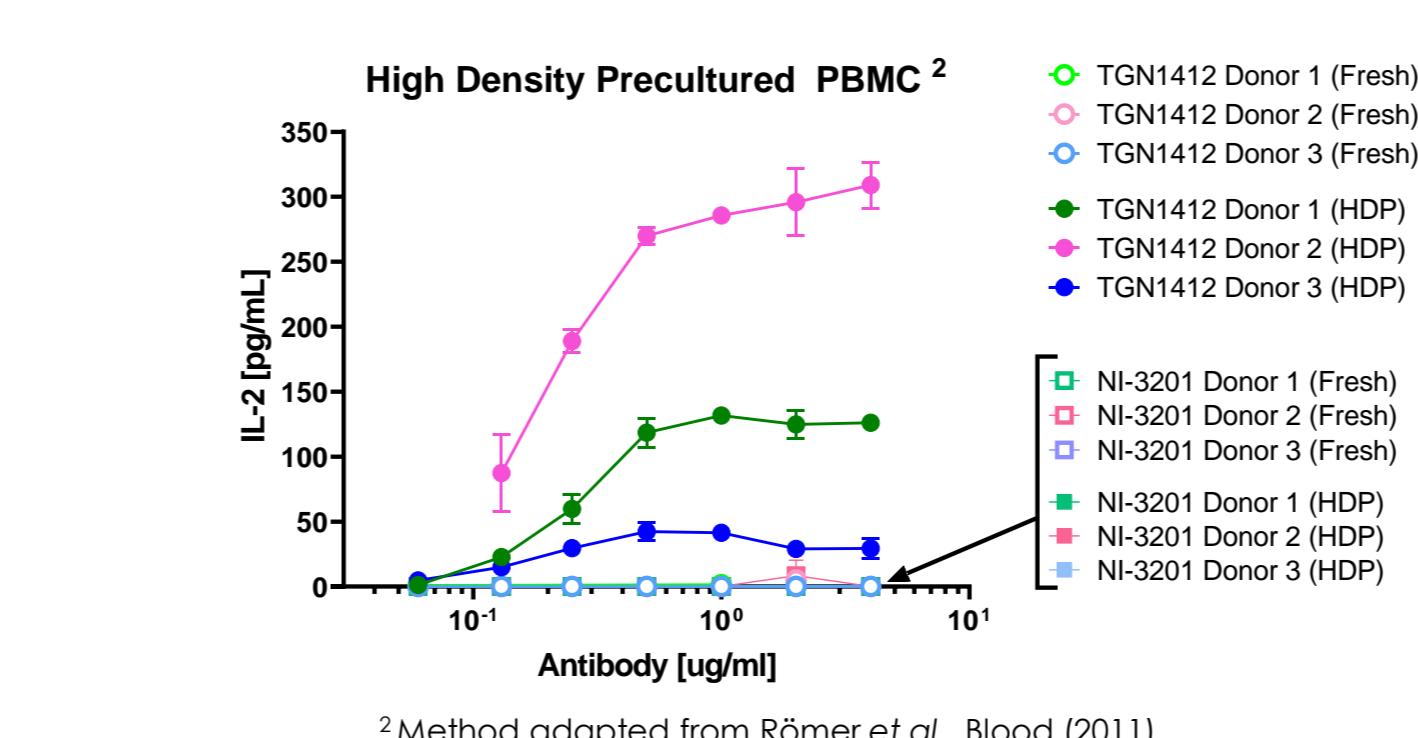
2. T cell activation by NI-3201 is signal 1 dependent and effective even at low E:T ratios
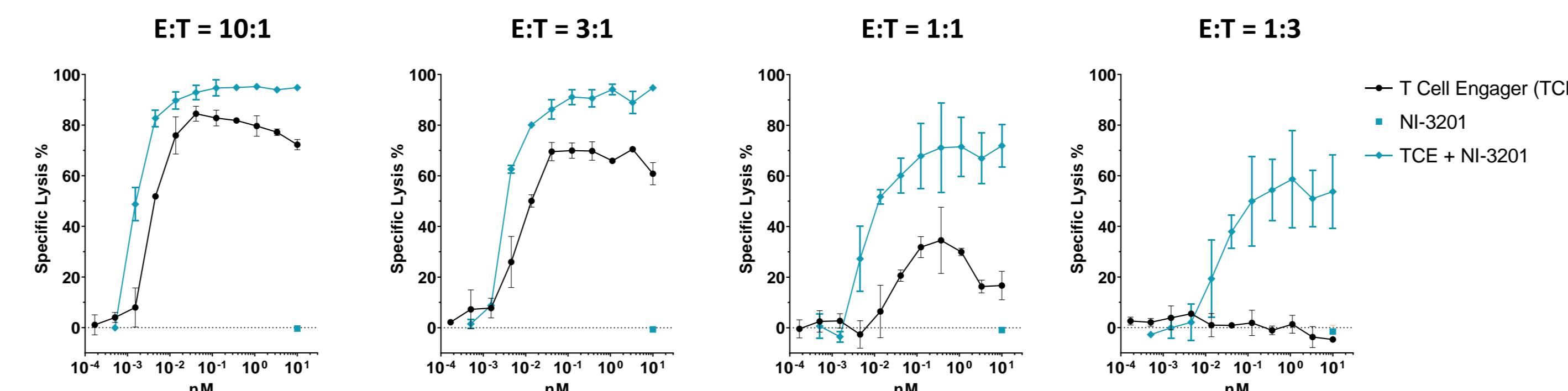
## NI-3201 shows single-agent anti-tumor activity in vivo

1. NI-3201 controls established MC38-hPD-L1 tumors in immunocompetent huCD28 mice
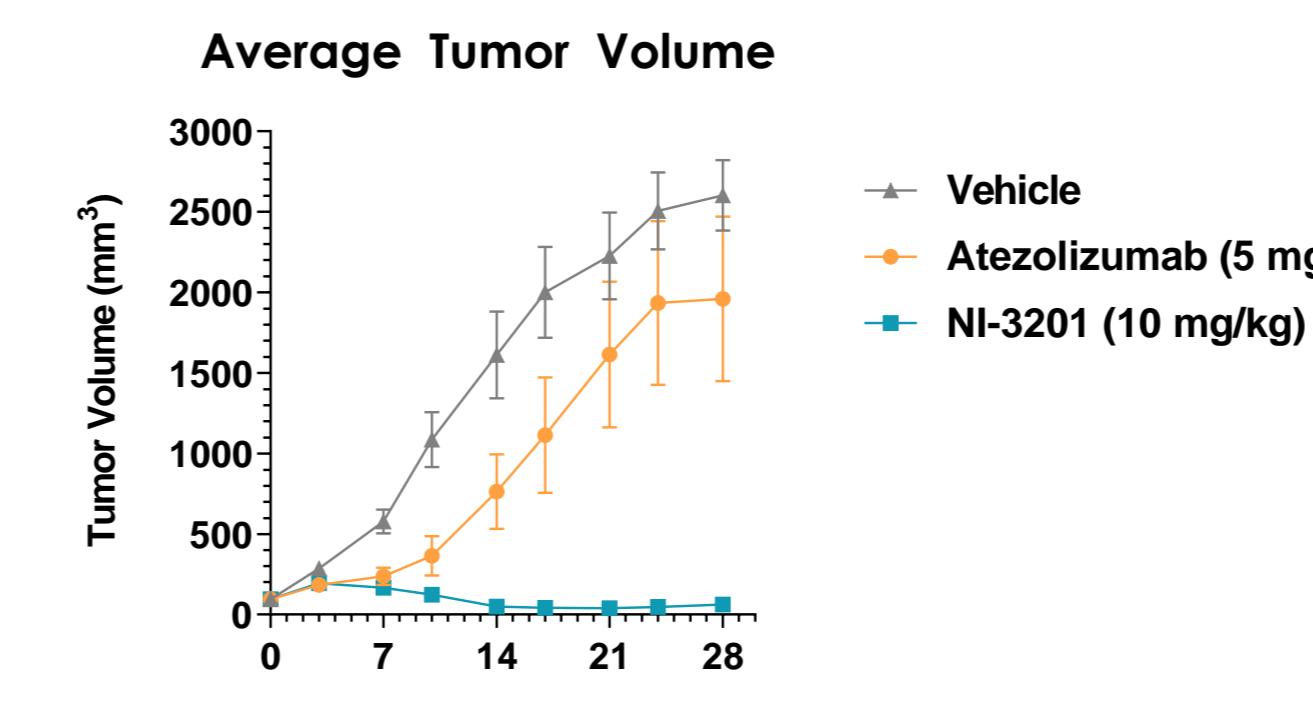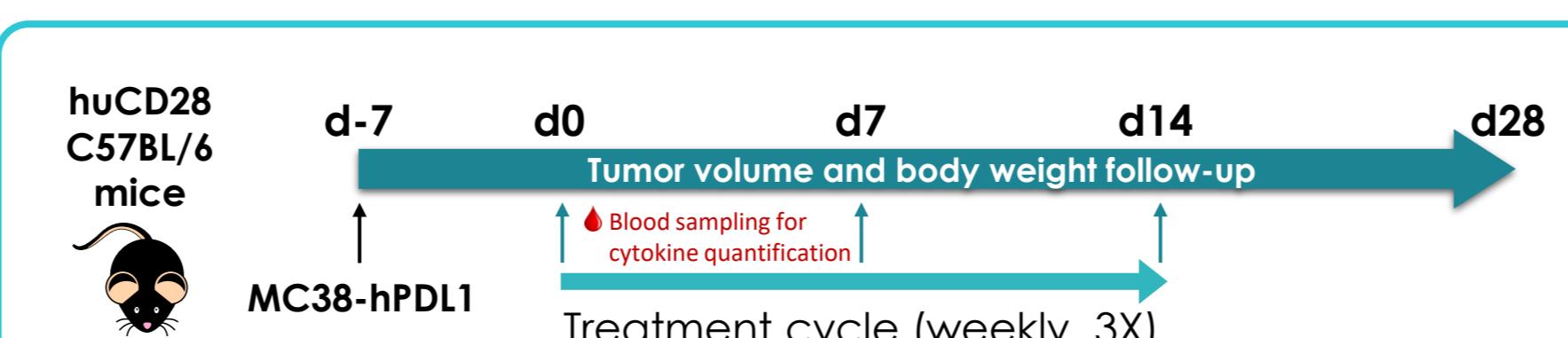
2. NI-3201 is well tolerated in immunocompetent huCD28 mice
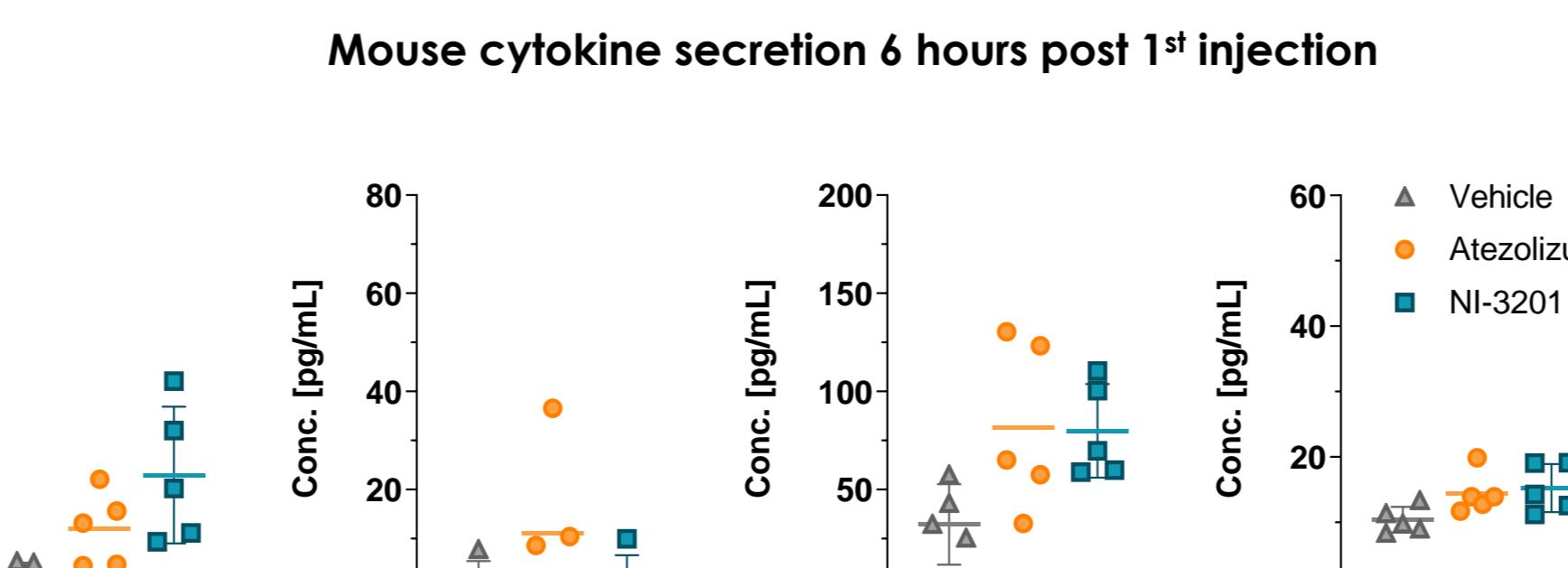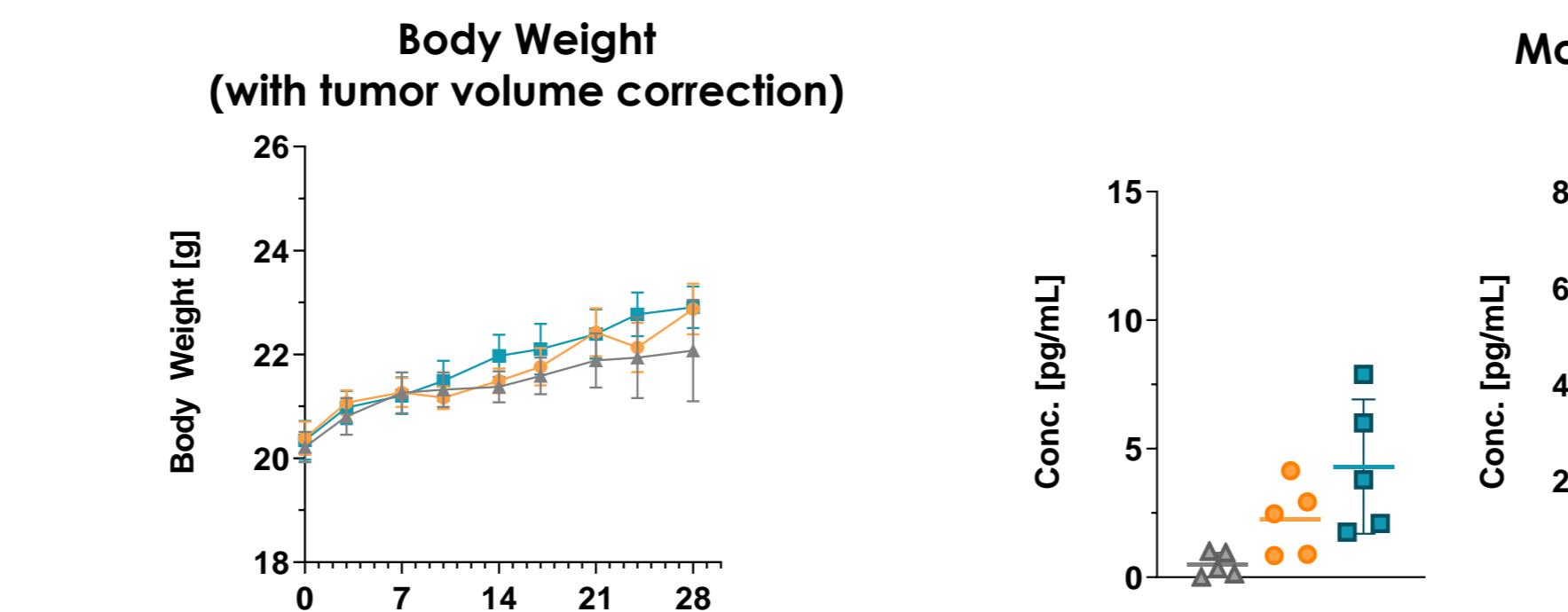
3. NI-3201 induces immunological memory against WT MC38
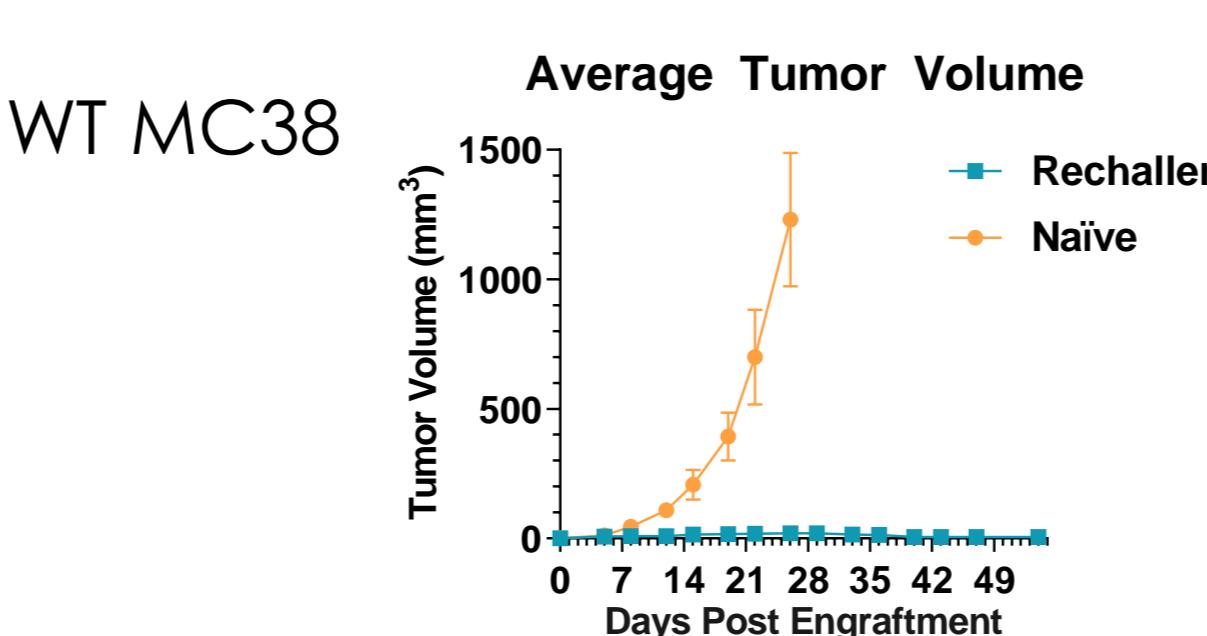
NI-3201 does not induce CD28-mediated CRS

1. NI-3201 is well tolerated in a model sensitive to CD28-mediated CRS
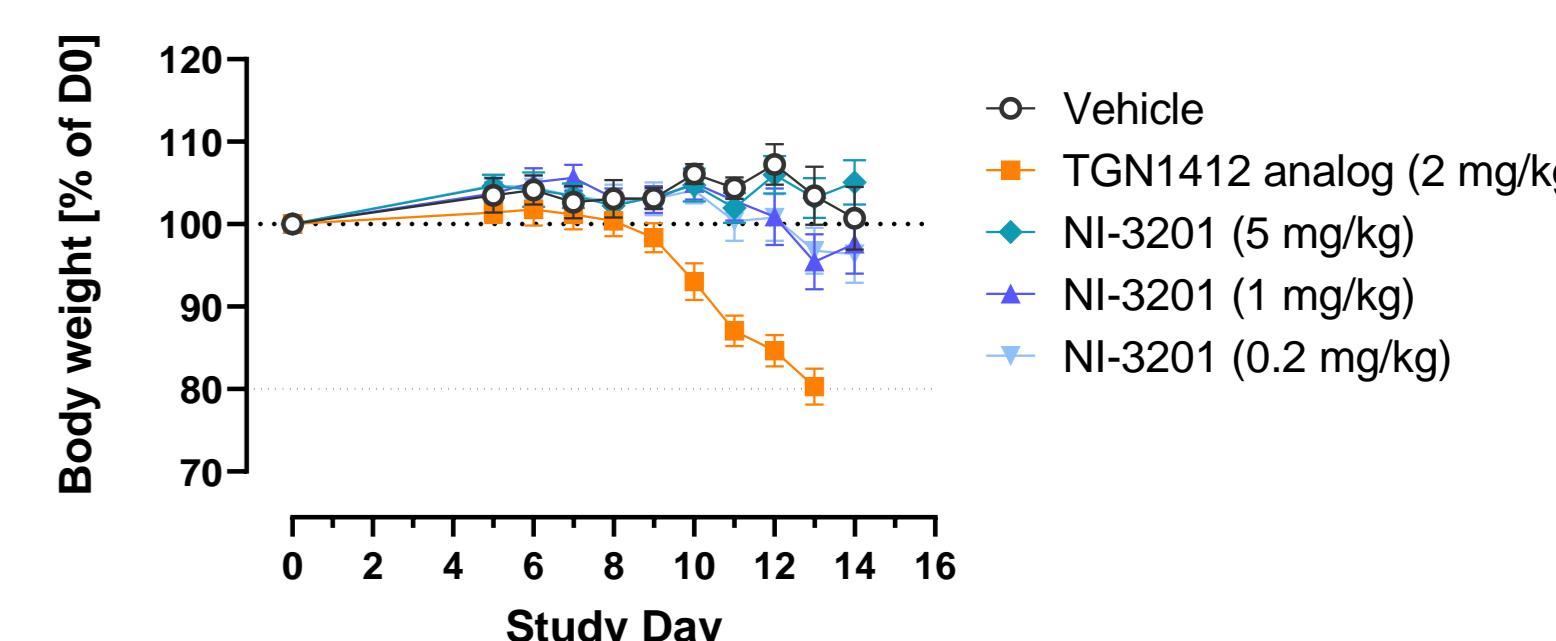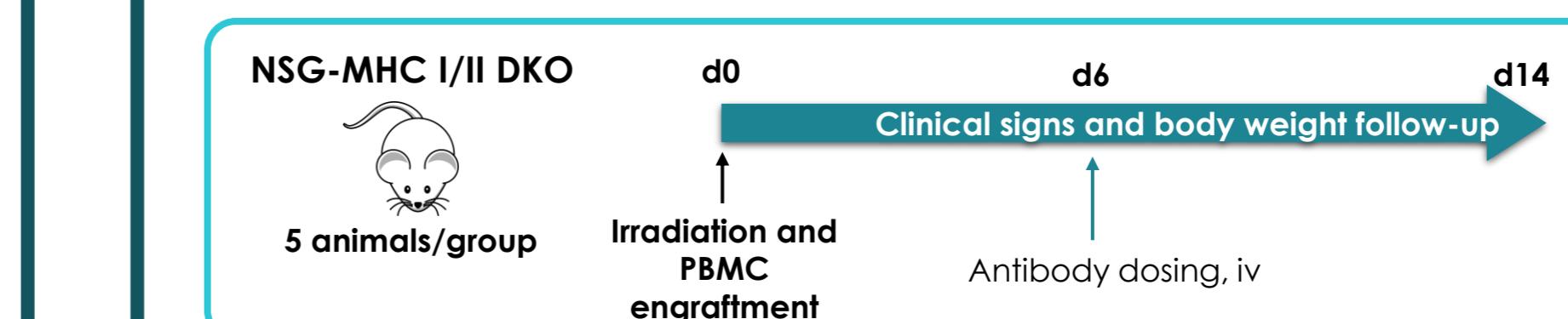
NI-3201 is well tolerated in cynomolgus monkeys

1. Ongoing NHP study suggests favorable pharmacokinetics
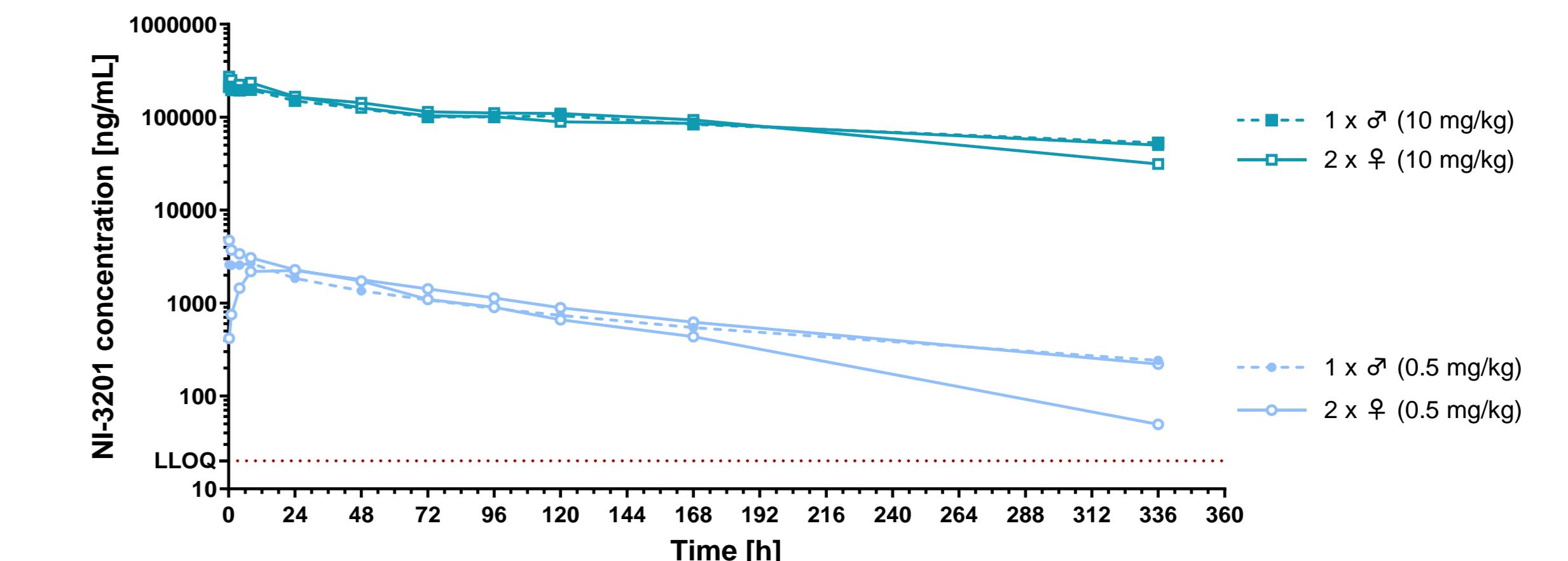
2. Upon NI-3201 administration to NHP, only a mild and transient IL-6 release was observed

IL-8, IL-10 and TNFα: measured below the LoD
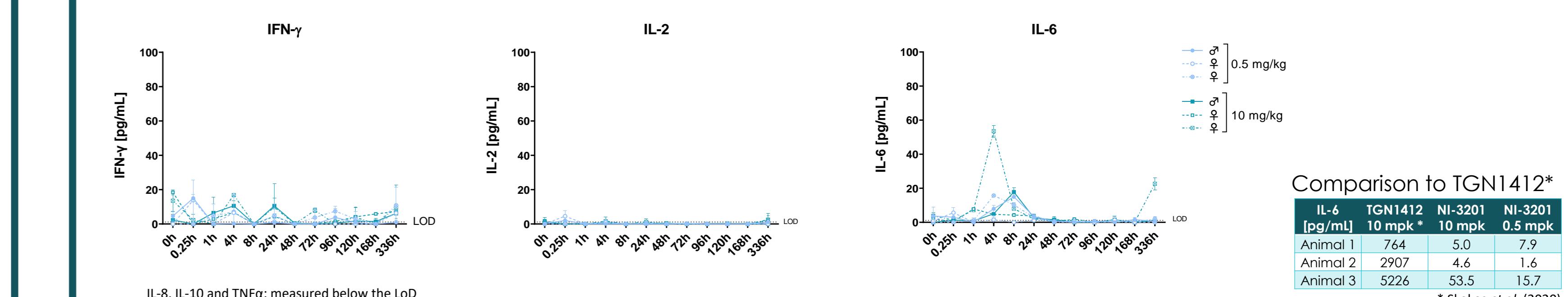
Comparison to TGN1412*

	IL-6 [pg/mL]	TGN1412 10 mpk *	NI-3201 10 mpk	NI-3201 0.5 mpk
Animal 1	764	5.0	7.5	
Animal 2	2907	4.6	1.6	
Animal 3	5226	53.5	15.7	

* Skokos et al. (2020)

Conclusions and Perspectives

- PD-L1 blockade to release the brake, CD28 agonistic activity to fuel the engine
- Universal combination partner enhancing T cell-mediated immunity to tumors
- Superior single-agent anti-tumor activity to PD-L1 mAb in vivo
- No flag raised in in vitro and in vivo safety studies
- Several other TAAxCD28 κλ bodies under development:

FcRH5 | HER2 | MSLN | GPC3 | CEA
Discovery | IND enabling | Phase I