NI-2601, an Fc-active CD47xPD-L1 bispecific antibody that selectively targets CD47 on PD-L1-positive cells

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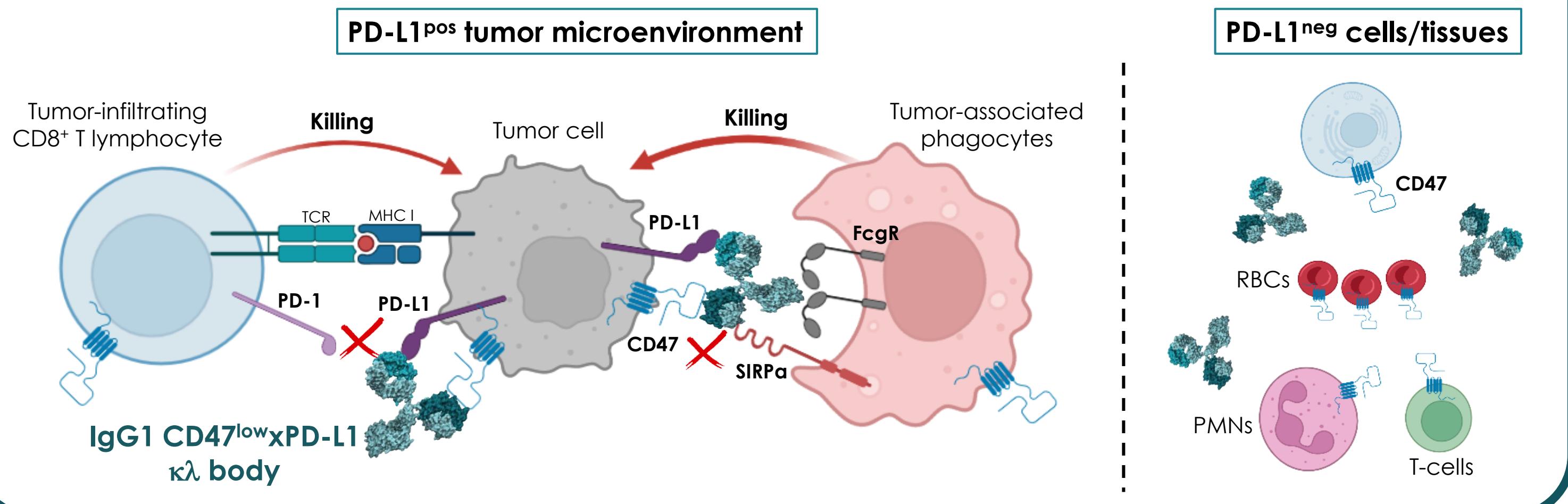
LIGHT CHAIN BIOSCIENCE
A brand of Novimmune SA
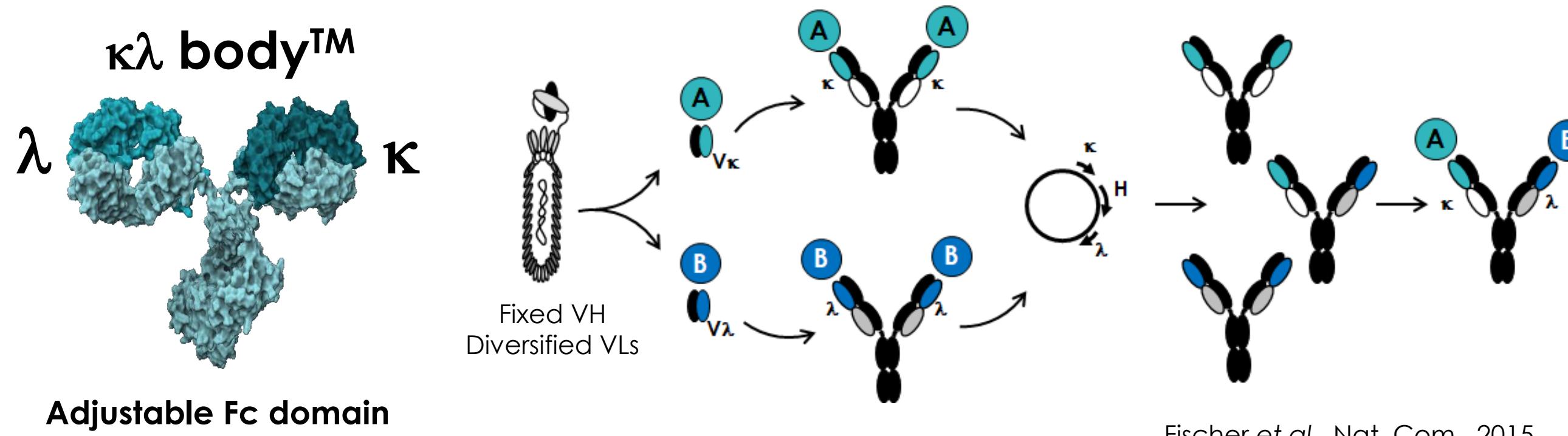
Background

- CD47/SIRPa innate checkpoint blockade mobilizes myeloid cells and can be combined to PD-1/PD-L1 T-cell checkpoint to eliminate cancer cells

- CD47xPD-L1 bsAbs· are being developed for guided inhibition of CD47 on PD-L1-positive cells, for efficient TME targeting and reducing the safety and PK issues faced by (monospecific) CD47 mAbs

PD-L1pos tumor microenvironment

PD-L1neg cells/tissues

Tumor-infiltrating CD8+ T lymphocyte — Killing — Tumor cell — Killing — Tumor-associated phagocytes

IgG1 CD47lowxPD-L1 κλ body

κλ body platform – Native, human bsAbs
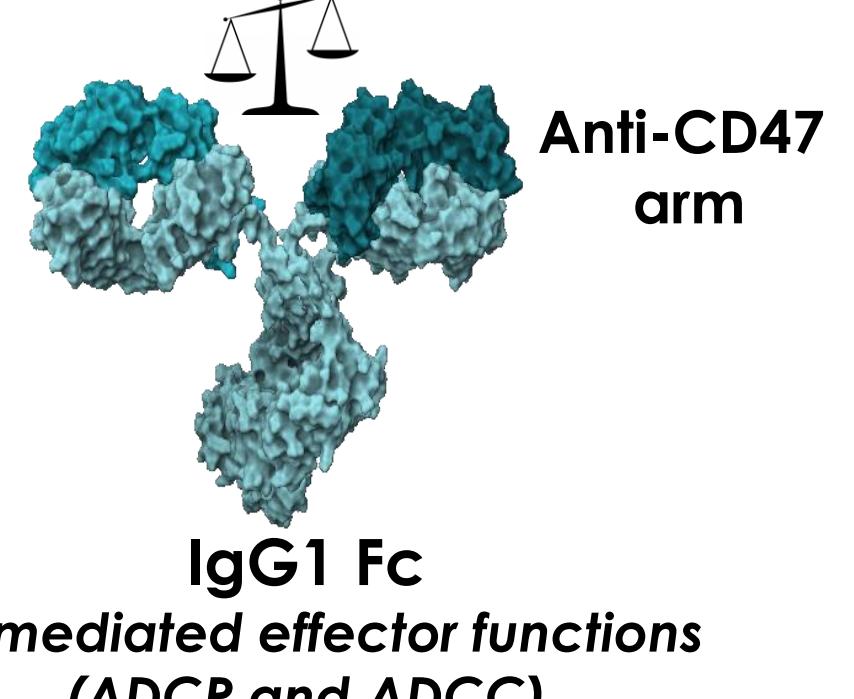
- Native, non-engineered, human bispecific antibodies
- Standard antibody discovery using common heavy chain libraries, kappa and lambda variable light chains drive the specificity to the targets
- Platform purification process, several GMP batches produced
- Two IgG1 CD47lowxTAA bsAbs in clinical development and multiple κλ bodies in preclinical development

κλ body™

Fixed VH Diversified VLs

Adjustable Fc domain

Fischer et al., Nat. Com., 2015
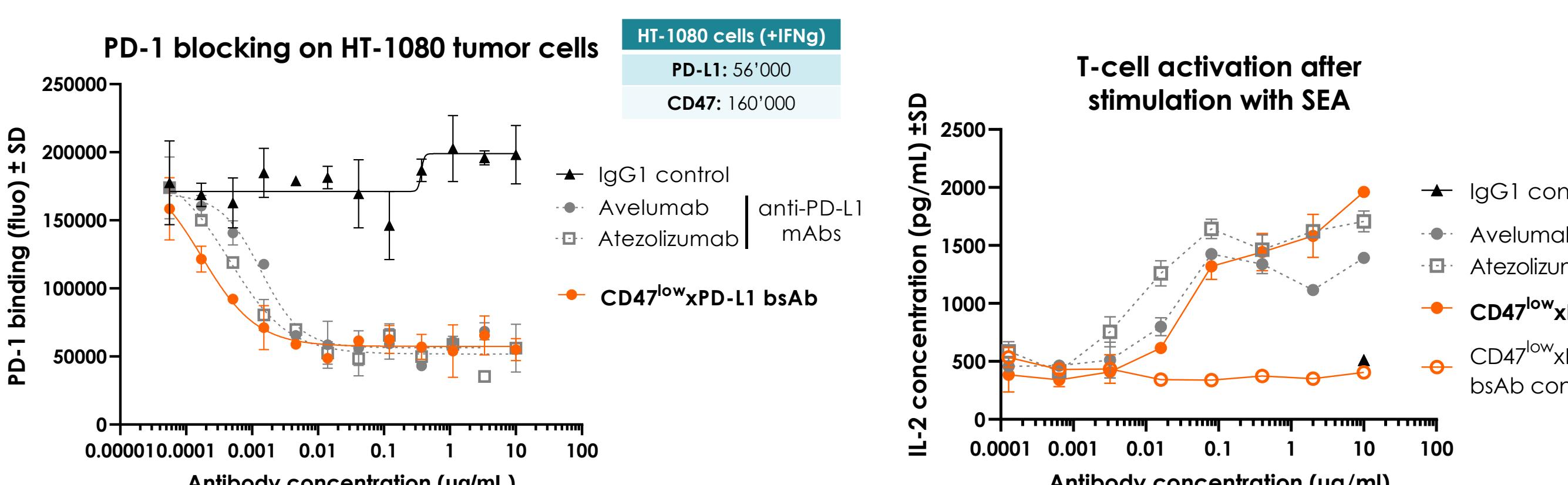
NI-2601, a CD47lowxPD-L1 IgG1 κλ body

NI-2601

Anti-PD-L1 arm   Anti-CD47 arm

IgG1 Fc
Fc-mediated effector functions (ADCP and ADCC)

- **Subnanomolar affinity**
- Blocks PD-1/PD-L1 axis
- Cross-reacts with cynomolgus

- **Low affinity ($K_D \approx 0.5\mu M$)**
- Blocks CD47/SIRPa axis on PD-L1pos cells
- Cross-reacts with cynomolgus

- Low-affinity CD47 arm prevents binding and killing of RBC and PD-L1neg cells
- PD-L1-guided binding and inhibition of CD47/SIRPa checkpoint
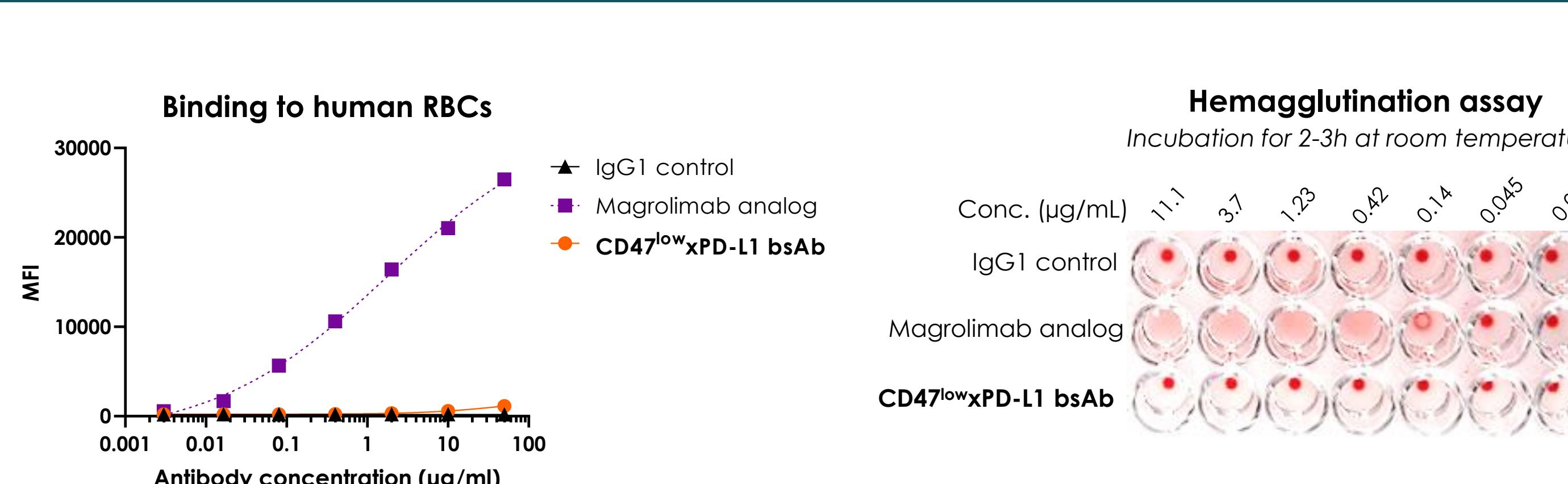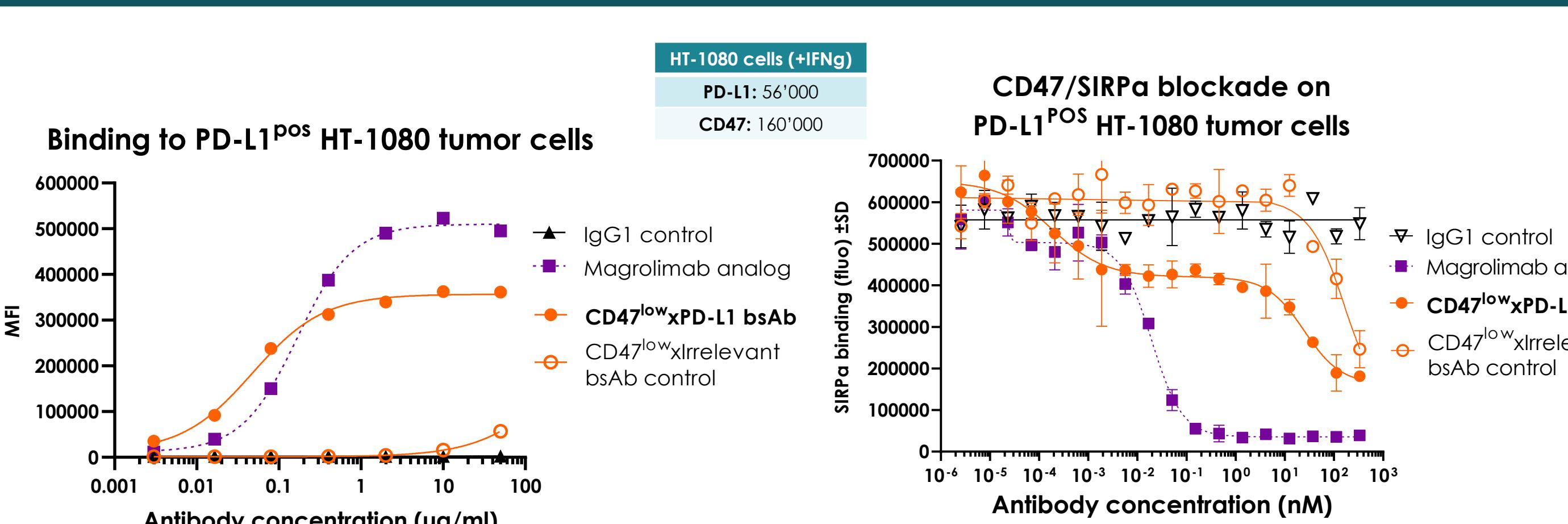
PD-1/PD-L1 blockade and enhancement of T-cell activation

PD-1 blocking on HT-1080 tumor cells

HT-1080 cells (+IFNg)
PD-L1: 56'000
CD47: 160'000

- IgG1 control
- Avelumab — anti-PD-L1 mAbs
- Atezolizumab
- CD47lowxPD-L1 bsAb

T-cell activation after stimulation with SEA

- IgG1 control
- Avelumab
- Atezolizumab
- CD47lowxPD-L1 bsAb
- CD47lowxIrrelevant bsAb control
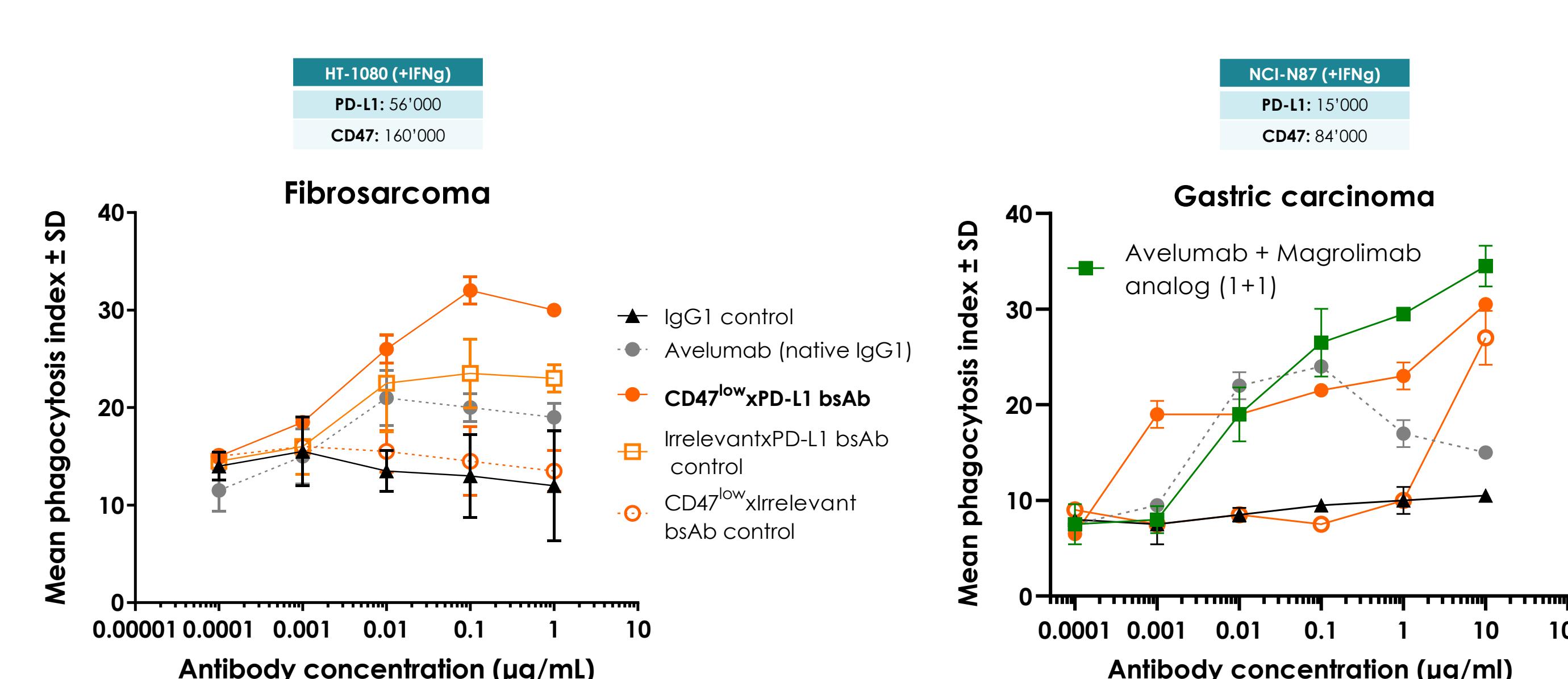
Residual binding to RBC and no induction of hemagglutination

Binding to human RBCs

- IgG1 control
- Magrolimab analog
- CD47lowxPD-L1 bsAb

Hemagglutination assay
Incubation for 2-3h at room temperature

Conc. (µg/mL)	11.1	3.7	1.23	0.42	0.14	0.045	0.015
IgG1 control							
Magrolimab analog							
CD47lowxPD-L1 bsAb							
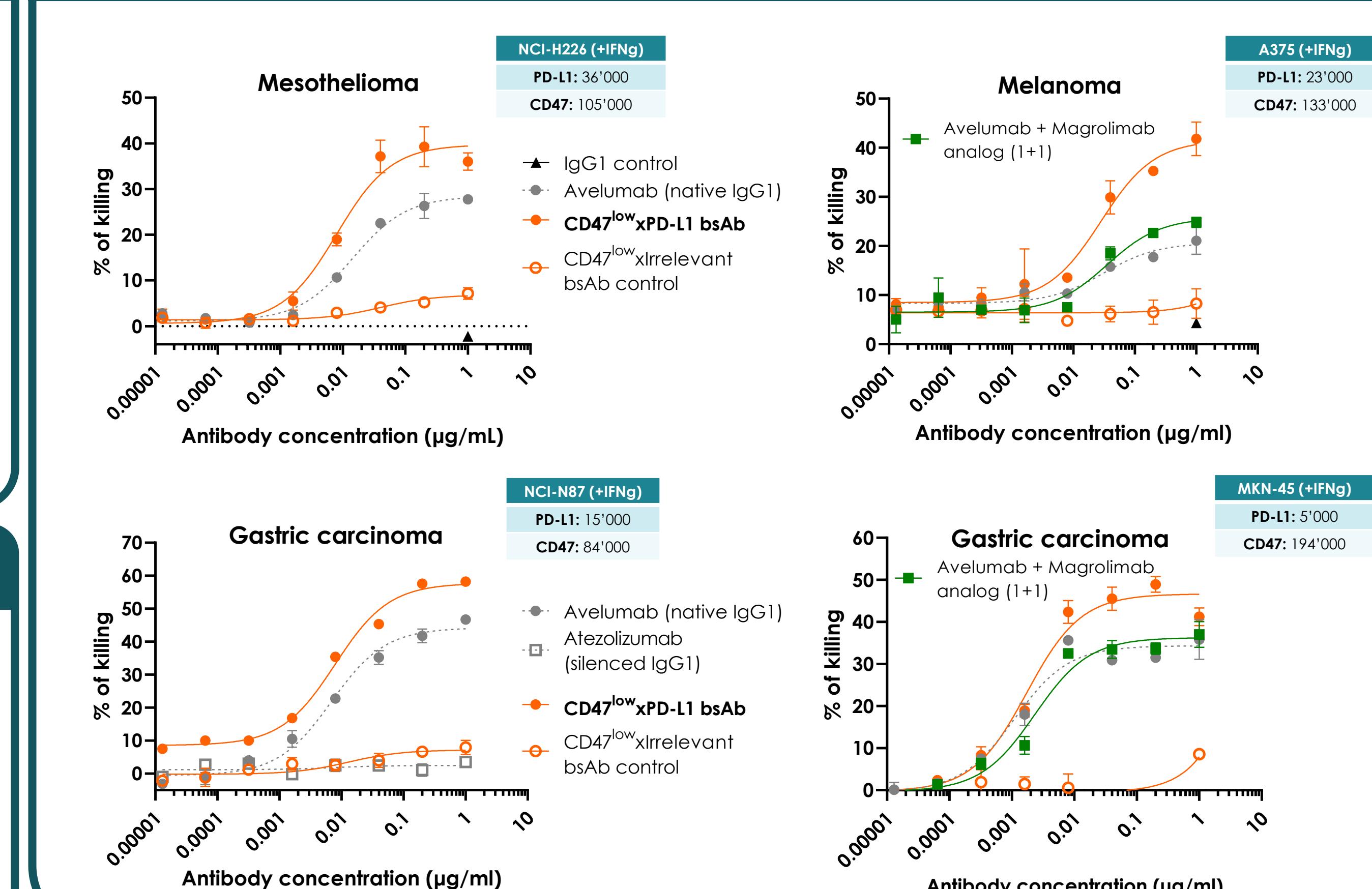
CD47/SIRPa blockade is driven by PD-L1 co-engagement

Binding to PD-L1pos HT-1080 tumor cells

HT-1080 cells (+IFNg)
PD-L1: 56'000
CD47: 160'000

- IgG1 control
- Magrolimab analog
- CD47lowxPD-L1 bsAb
- CD47lowxIrrelevant bsAb control

CD47/SIRPa blockade on PD-L1POS HT-1080 tumor cells

- IgG1 control
- Magrolimab analog
- CD47lowxPD-L1 bsAb
- CD47lowxIrrelevant bsAb control

ADCP of PD-L1pos tumor cells

Fibrosarcoma

HT-1080 (+IFNg)
PD-L1: 56'000
CD47: 160'000

- IgG1 control
- Avelumab (native IgG1)
- CD47lowxPD-L1 bsAb
- IrrelevantxPD-L1 bsAb control
- CD47lowxIrrelevant bsAb control

Gastric carcinoma

NCI-N87 (+IFNg)
PD-L1: 15'000
CD47: 84'000

- Avelumab + Magrolimab analog (1+1)

ADCC across a range of PD-L1pos tumor cell lines

Mesothelioma

NCI-H226 (+IFNg)
PD-L1: 36'000
CD47: 105'000

- IgG1 control
- Avelumab (native IgG1)
- CD47lowxPD-L1 bsAb
- CD47lowxIrrelevant bsAb control

Melanoma

A375 (+IFNg)
PD-L1: 23'000
CD47: 133'000

- Avelumab + Magrolimab analog (1+1)

Gastric carcinoma

NCI-N87 (+IFNg)
PD-L1: 15'000
CD47: 84'000

- Avelumab (native IgG1)
- Atezolizumab (silenced IgG1)
- CD47lowxPD-L1 bsAb
- CD47lowxIrrelevant bsAb control

Gastric carcinoma

MKN-45 (+IFNg)
PD-L1: 5'000
CD47: 194'000

- Avelumab + Magrolimab analog (1+1)

No significant cytokine release in whole blood

- The CD47lowxPD-L1 bsAb and controls were incubated in whole blood from healthy donors (n=5-10 donors) for 24h before measurement of IL-6 and IFNg in supernatants

IL-6 concentration in supernatant

IFNg concentration in supernatant

Conclusions

- **NI-2601, an Fc-active CD47lowxPD-L1 bispecific antibody, generated using the κλ body phage display platform:**
  - Spares binding to RBC and preferentially blocks CD47/SIRPa on PD-L1-positive cells
  - Increases T-cell activation and mediates PD-L1-positive tumor cell killing through ADCP and ADCC
  - Good safety profile expected based on preclinical data in non-human primates with Fc-active CD47lowxTAA bsAbs

- **For partnering opportunities, please reach out to bd@lightchainbio.com**

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