Abstract 265

NI-2601 and NI-2901: PD-L1xCD47 bispecific antibodies for cancer therapy

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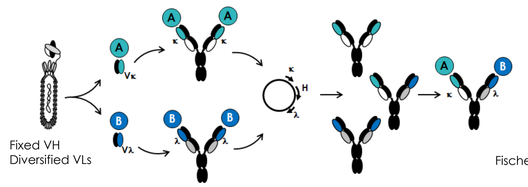
Background

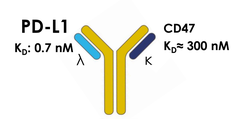
- Two distinct PD-L1xCD47 bsAb approaches to enable preferential blockade of PD-1/PD-L1 and CD47/SIRPa immune checkpoints in the tumor microenvironment and limit safety and bioavailability concerns associated with anti-CD47 mAbs
- The bsAbs, having different CD47 arm affinities and IgG Fc portions, were generated using the κλ body™ phage display platform:
  - Native, non-engineered, human bispecific antibodies
  - Standard antibody discovery using common heavy chain libraries
  - κλ bodies assembly: 2 identical heavy chains and 2 different light chains: one kappa, one lambda



Fischer *et al.*, Nat. Com., 2015

Two PD-L1xCD47 bsAb approaches

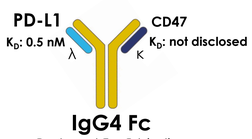
PD-L1xCD47^{low} bsAb (NI-2601)



IgG1 Fc
High FcγR binding
ADCP+++ and ADCC+++

- Low affinity to CD47 prevents monovalent binding to PD-L1-negative cells
- PD-L1-guided inhibition of CD47/SIRPa
- High Fc-mediated effector functions

PD-L1xCD47^{high} bsAb (NI-2901)

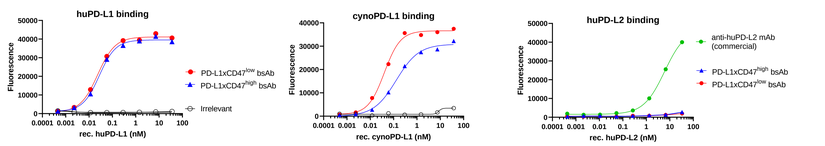


IgG4 Fc
Reduced FcγR binding
ADCP+

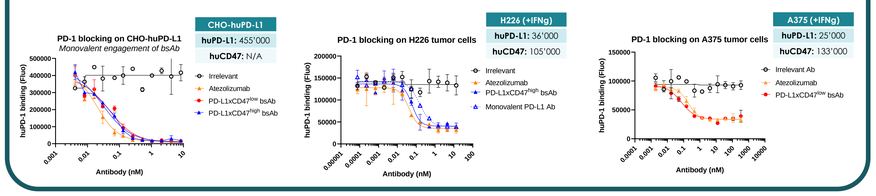
- Fine-tuned CD47 arm affinity to moderate binding to red blood cells and platelets
- CD47/SIRPa inhibition reinforced by PD-L1 co-engagement
- Low Fc-mediated effector functions

PD-L1 binding and PD-1/PD-L1 blocking

- **PD-L1xCD47 bsAbs bind to human PD-L1, are cross-reactive to cynomolgus and do not bind human PD-L2**

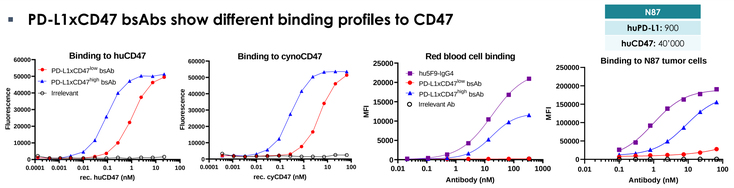


- **PD-L1xCD47 bsAbs block PD-1/PD-L1 interaction similar to atezolizumab**

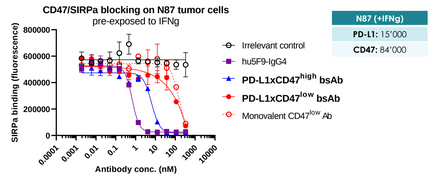


CD47 binding and CD47/SIRPa blocking

- **PD-L1xCD47 bsAbs show different binding profiles to CD47**

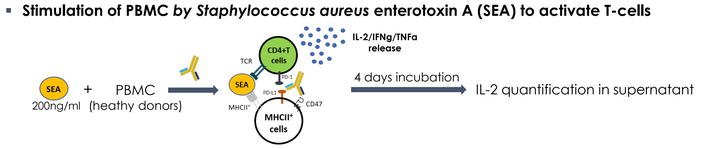


- **While PD-L1xCD47^{high} bsAb can effectively block CD47/SIRPa interaction independently of PD-L1 co-engagement, PD-L1xCD47^{low} bsAb will preferentially block CD47 once PD-L1 is engaged**

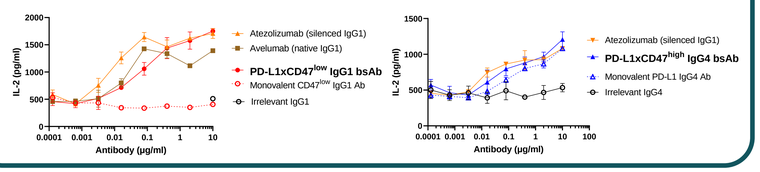


T-cell activation

- **Stimulation of PBMC *by Staphylococcus aureus* enterotoxin A (SEA) to activate T-cells**

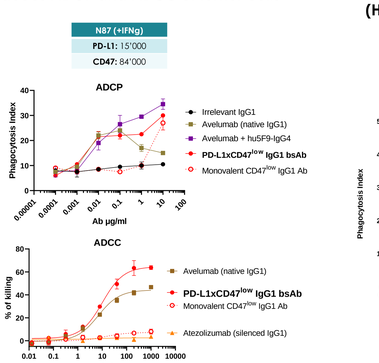


- **T-cell activation is significantly enhanced with both bispecific approaches, similar to the anti-PD-L1 benchmarks**

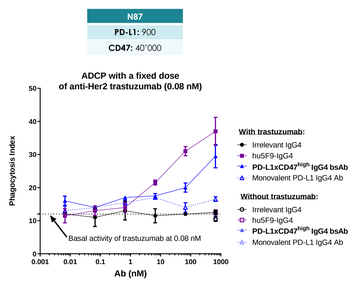


Fc-mediated effector function (ADCP, ADCC)

- **PD-L1xCD47^{low} bsAb with IgG1 Fc portion induces ADCP and ADCC of tumor cells**

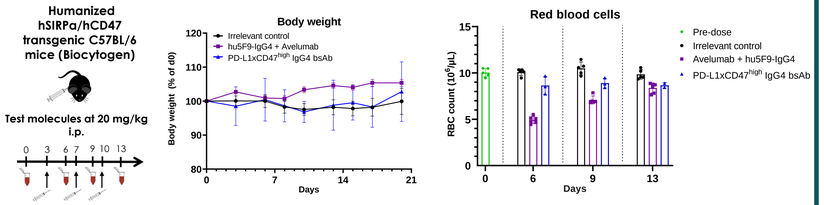


- **PD-L1xCD47^{high} bsAb with IgG4 Fc portion enhances ADCP induced by trastuzumab (Herceptin®)**

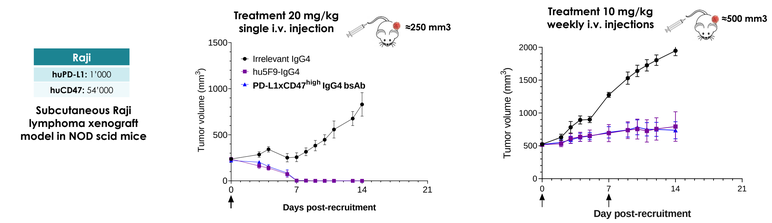


Tolerability and activity of the high-affinity CD47 arm *in vivo*

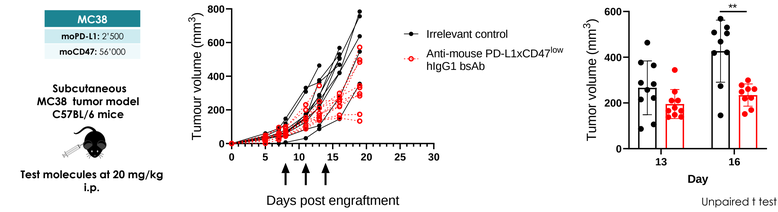
- **The CD47 arm of PD-L1xCD47^{high} bsAb is well-tolerated and does not cause anemia**



- **The CD47 arm of PD-L1xCD47^{high} bsAb shows activity in a xenograft model**

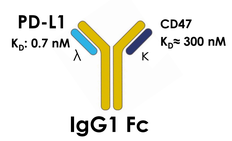


Surrogate PD-L1xCD47^{low} bsAb activity *in vivo*



Conclusions and Perspectives

PD-L1xCD47^{low} bsAb (NI-2601)



IgG1 Fc

- PD-L1-guided inhibition of CD47/SIRPa
- Fc-mediated killing of PD-L1^{+} cells
- Activity *in vivo* of a mouse surrogate

PD-L1xCD47^{high} bsAb (NI-2901)

IgG4 Fc

- Blockade of PD-1/PD-L1 and CD47/SIRPa
- Tolerability and activity of the CD47 arm *in vivo*
- Potential combination option with approved anti-TAA mAbs (e.g. trastuzumab, cetuximab)

- **NI-2601 and NI-2901 lead candidates have been identified, non-human primate studies and stable cell-line construction for GMP manufacture will start early 2022**
- **For partnering opportunities, please reach out to bd@lightchainbio.com**

SITC Annual Meeting, November 10-14 2021, Washington, D.C., USA

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