

AN AFFINITY-OPTIMIZED CD47XPD-L1 BISPECIFIC ANTIBODY FOR DUAL IMMUNE CHECKPOINT BLOCKADE

¹Xavier Chaudet, ¹Sebastien Calloud, ¹Margaux Legrand, ¹Laura Cons, ¹Laurence Chatel, ¹Adeline Lesnier, ¹Nicolas Bosson, ¹Pauline Lloveras, ¹Pauline Malinge, ¹Ulla Ravn, ¹Valery Moine, ¹Bruno Daubeuf, ¹Yves Poitevin, ¹Giovanni Magistrelli, ¹Susana Salgado-Pires, ²Dmitry Shchelokov, ²Oleg Demin, ¹Limin Shang, ¹Krzysztof Masternak, ¹Walter Ferlin*. ¹Light Chain Bioscience-Novimmune SA, Geneva, Switzerland; ²InsysBio UK Ltd, Edinburgh, UK

Background To enhance efficacy of anti-PD-1/PD-L1 antibodies, many combinations with various therapeutic agents are being investigated. Blocking the CD47/SIRP α checkpoint with monoclonal antibodies (mAbs) or decoy receptors is emerging as an effective approach to mobilize myeloid cells and support T-cell mediated antitumor responses. The benefit of combining CD47/SIRP α and PD-1/PD-L1 blockade to improve tumor control has been demonstrated in preclinical models and is being explored in patients. However, CD47 mAbs are hindered by ubiquitous CD47 expression leading to pharmacokinetic (PK) and safety issues.

Methods NI-2901, an IgG4 CD47xPD-L1 bsAb of optimized affinity, was generated using the $\kappa\lambda$ body platform.¹ *In vitro* assays were used to characterize its binding profile and checkpoint inhibition as well as its capacity to enhance T-cell activation and macrophage-mediated phagocytosis of tumor cells. PD-L1-independent CD47 antitumor activity was assessed *in vivo* in a PD-L1-negative xenograft model and compared to the humanized IgG4 anti-CD47 antibody, magrolimab. PK and tolerability of NI-2901 were evaluated in non-human primates (NHP), allowing for comprehensive modeling and simulations in humans.

Results Consistent with its intermediate CD47 affinity, NI-2901 shows low binding to red blood cells as compared to anti-CD47 mAbs and induces CD47/SIRP α blockade on PD-L1-negative cells, that is significantly enhanced once PD-L1 is expressed. As a result, the bsAb is able to enhance the phagocytosis of PD-L1-negative and -positive tumor cell lines induced by mAbs targeting tumor-associated antigens (e.g. CD20, HER2 and CD19) and demonstrates *in vivo* anti-tumor activity in the Raji B-cell lymphoma xenograft model. Given its high affinity for PD-L1, NI-2901 triggers effective blockade of the PD-1/PD-L1 interaction on cells, inducing T-cell activation *in vitro* similar to the anti-PD-L1 antibodies, atezolizumab and avelumab. After 4-weekly 30mg/kg injections in NHP, NI-2901 was well-tolerated showing no signs of hemotoxicity, while magrolimab induced a significant drop in RBC after a single 10mg/kg injection. Translational PK modelling and simulations from NHP to human suggest a more favorable dosing regimen is possible as compared to benchmark CD47-targeted approaches.

Conclusions As a dual immune checkpoint inhibitor, NI-2901 triggers effective T-cell activation, enhances phagocytosis of tumor cells and is expected to have improved efficacy over PD-1/PD-L1 blockade alone. The bsAb is well-tolerated in NHP at predicted therapeutic doses without inducing RBC or platelet depletion.

REFERENCE

1. Fischer N, *et al.* Exploiting light chains for the scalable generation and platform purification of native human bispecific IgG. *Nat. Commun.* 2015 May;6(1):6113.

Ethics Approval Studies in mouse models were performed at the sponsor's animal facility in accordance with the Swiss Federal Veterinary Office guidelines and approved by the animal

research committee of the Geneva canton, Switzerland (ID numbers: GE43 and GE/131/19)

Studies in non-human primates were outsourced and performed by Accelerera S.r.l., Italy and approved by the local Animal Welfare Body before approval by the Italian Ministry of Health (ID number: 215/2021-PR)

<http://dx.doi.org/10.1136/jitc-2022-SITC2022.0481>