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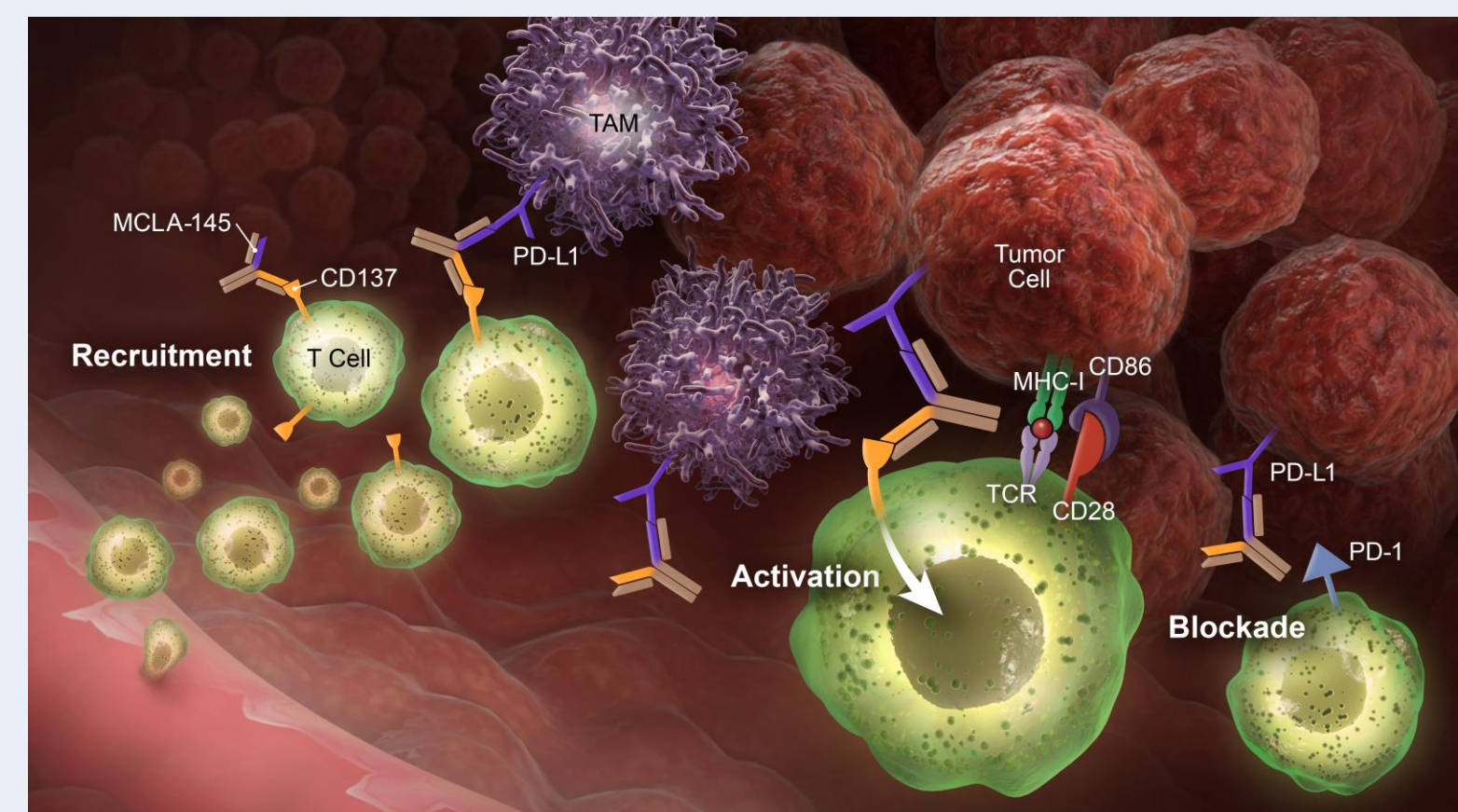
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## Abstract

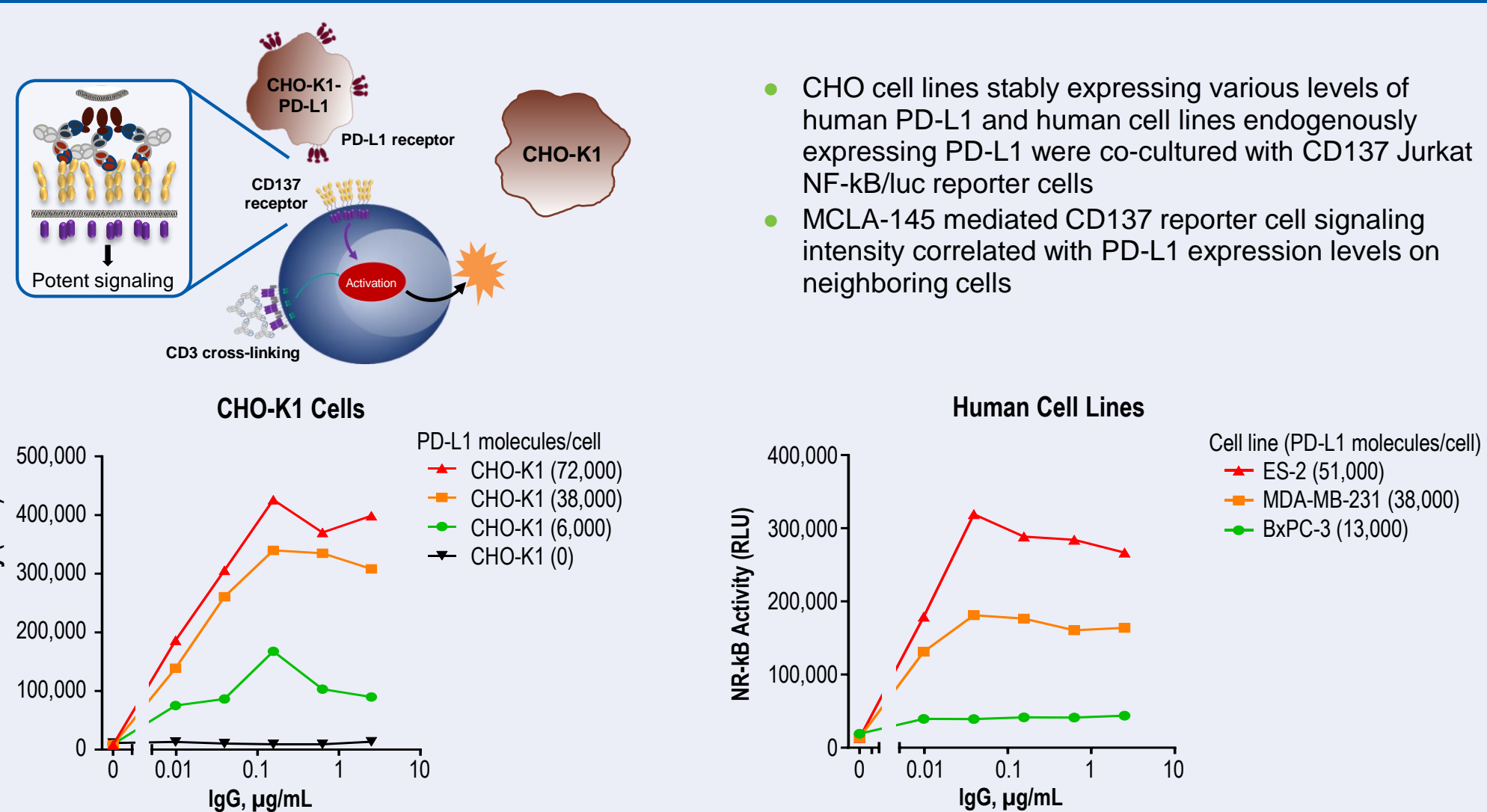
CD137 (4-1BB) is a transmembrane costimulatory receptor on T and NK cells that enhances adaptive immune responses and is a critical mediator of antitumor immunity. The development of CD137 targeted agents for cancer therapy has been hampered by on-target off-tumor toxicity in the case of agonist monospecific, bivalent mAbs or limited antitumor activity in the case of crosslinking mAbs. Here we have developed an Fc-silenced bispecific IgG1 antibody to CD137 and PD-L1 with monovalent binding specificity to each target. MCLA-145 drives transactivation of CD137 in the vicinity of cells expressing PD-L1, such as in the immunosuppressive tumor microenvironment. The degree of CD137 agonistic activity in T cells correlated with the expression level of PD-L1 on neighboring cells, as demonstrated in transactivation assays whereby reporter T cells were co-cultured with cells expressing different levels of PD-L1. PD-L1 expression as low as 6000 receptors per cell was sufficient to activate CD137 in neighboring T cells. In contrast, MCLA-145 blocked PD-1 signaling without requirement for CD137 binding in a PD-1/PD-L1 reporter assay. CD137 signaling was induced by MCLA-145 in multiple primary human immune cell assays including the mixed lymphocyte reaction, human PBMC, and whole blood SEB stimulation assays. MCLA-145 reversed T cell suppression mediated by M2 macrophages or Tregs, in vitro. In addition, MCLA-145 enhanced Ag-specific expansion and differentiation of human naive CD8<sup>+</sup> T cells in vitro. In vivo, MCLA-145 treatment resulted in significant tumor immune activation and antitumor responses in 2 separate humanized mouse tumor models. In one model, human T cells expressing NY-ESO specific TCR were adoptively transferred to mice bearing A549 tumors, which expressed NY-ESO antigen and human PD-L1. MCLA-145 treatment at 5 mg/kg resulted in 54% tumor growth inhibition (TGI) as compared to T cell only-treated mice. In the tumors of MCLA-145-treated mice, the percentage of NY-ESO specific CD8<sup>+</sup> T cells were significantly increased compared with controls. In a second model, mice engrafted with human CD34<sup>+</sup> cells were implanted with the breast tumor cell line MDA-MB-231. MCLA-145 at 0.5 mg/kg and 5 mg/kg induced significant tumor growth inhibition (55% and 57%, respectively) as compared to vehicle control or Fc-silenced hulgG1 controls. Additionally, 2 out of 9 animals in the 5 mg/kg MCLA-145-treated group had complete tumor regression. MCLA-145 increased the number of infiltrating CD8<sup>+</sup> T cells, as well as the percentage of central memory CD8<sup>+</sup> T cells. The cured animals were then re-challenged with MDA-MB-231 tumor cells, and tumors of previously cured mice were rejected as compared to no growth inhibition in treatment-naïve CD34<sup>+</sup> NSG mice. In conclusion, these data support the clinical evaluation of MCLA-145 as a novel, PD-L1 dependent CD137 agonist immune therapy.

## Introduction

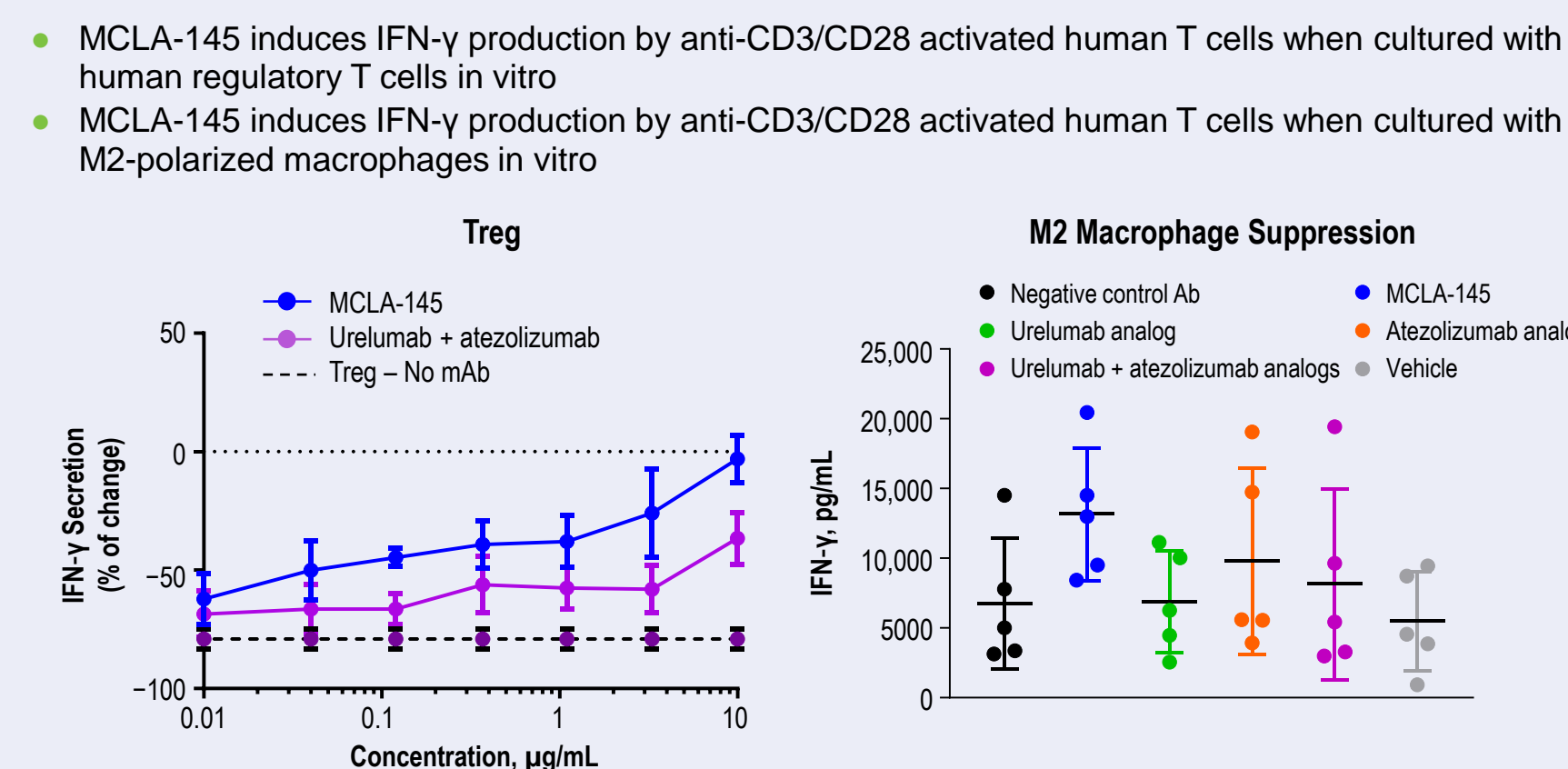
- CD137 (4-1BB) is a transmembrane costimulatory receptor on T and NK cells that enhances adaptive immune responses and is a critical mediator of antitumor immunity
- The development of CD137-targeted agents for cancer therapy has been hampered by on-target off-tumor toxicity
- CD137 signaling requires receptor clustering by the trimeric CD137 ligand, agonistic monoclonal antibodies (mAbs), or indirectly via cross-linking of CD137 binding antibodies by Fcγ receptors on neighboring cells
- PD-L1 expression is frequently observed on tumor cells, and mAb-based PD-L1 inhibitors have demonstrated durable tumor remission in patients with diverse advanced cancers in the clinic
- MCLA-145 is a Biclonic<sup>®</sup> T cell agonist that binds with high affinity and specificity to human PD-L1 and CD137



## MCLA-145 Activity Correlates With PD-L1 Expression Levels

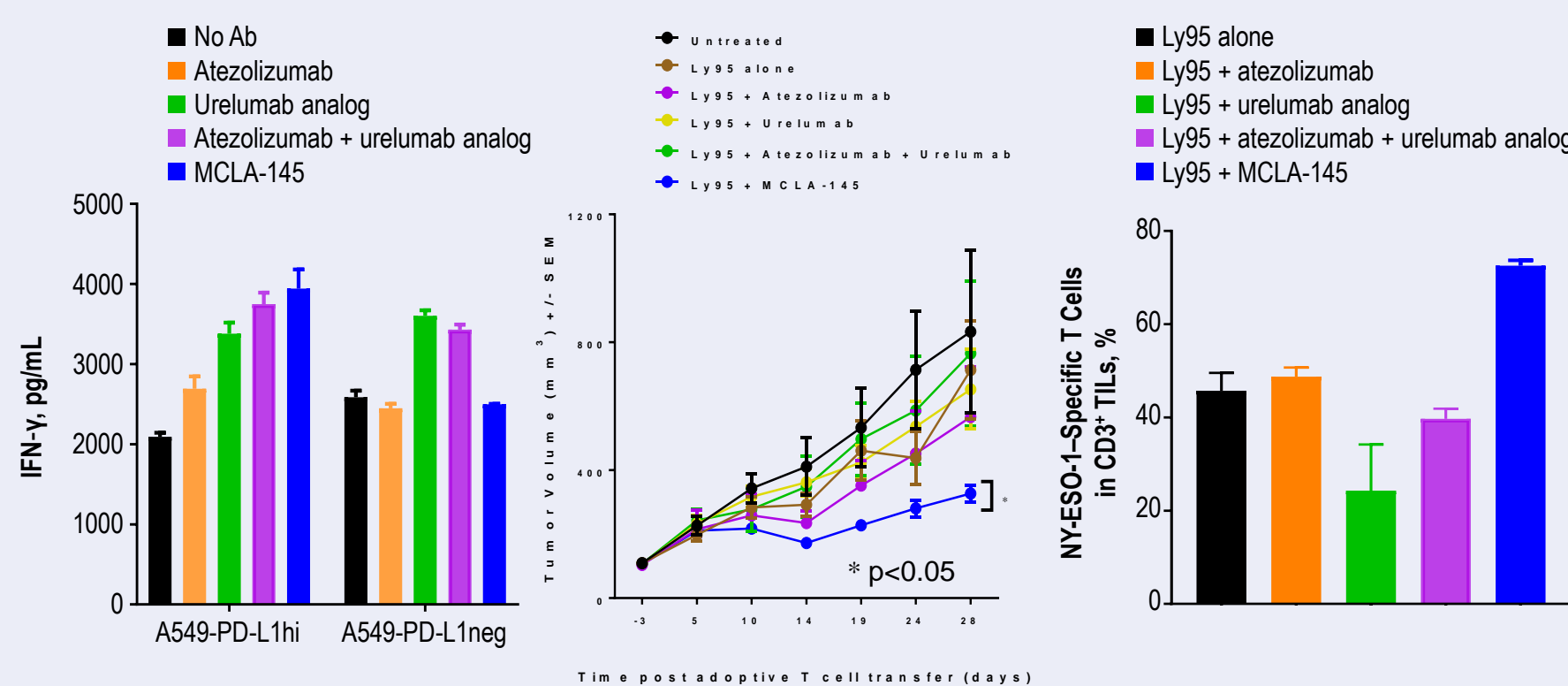


## MCLA-145 Reverses M2 Macrophage and Treg Suppression

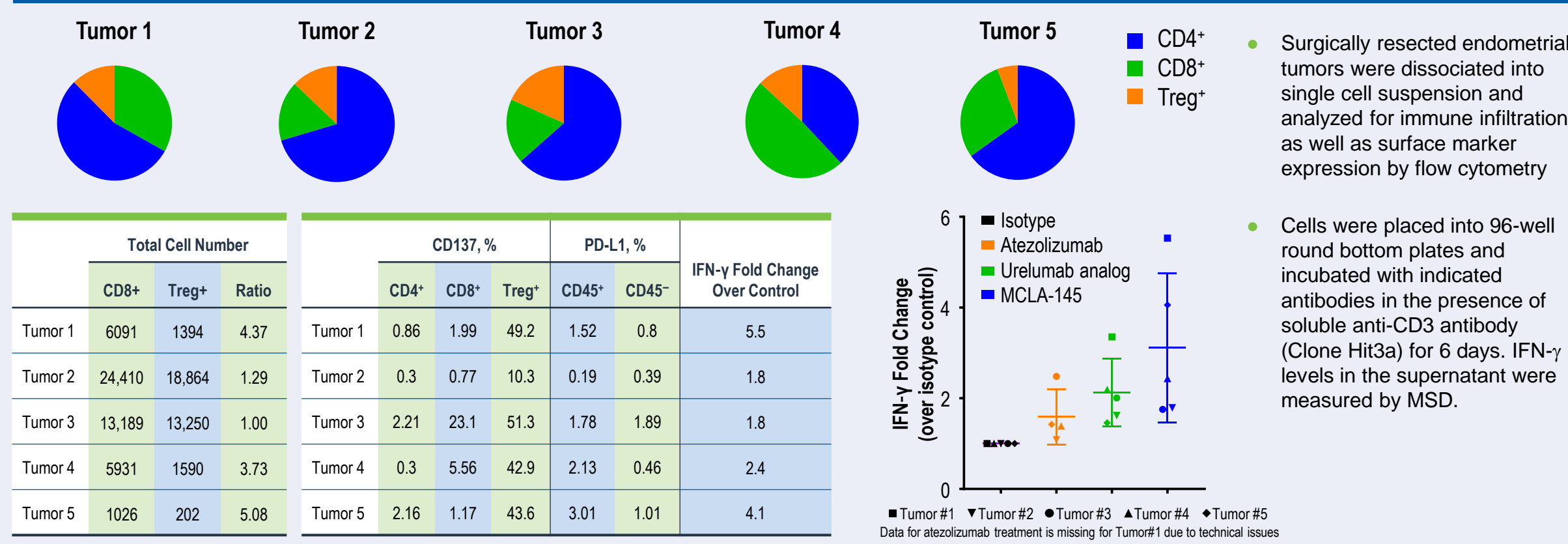


## Ly95-NY-ESO Adoptive T Cell Transfer Model

- MCLA-145 induces IFN-γ production in NY-ESO-1-specific T cells (Ly95 cells) co-cultured with NY-ESO-1+ A549 cells 72 hours
- MCLA-145 enhances the antitumor activity and tumor infiltration of NY-ESO-1-specific T cells in NSG mice implanted with NY-ESO-1+ A549 tumors

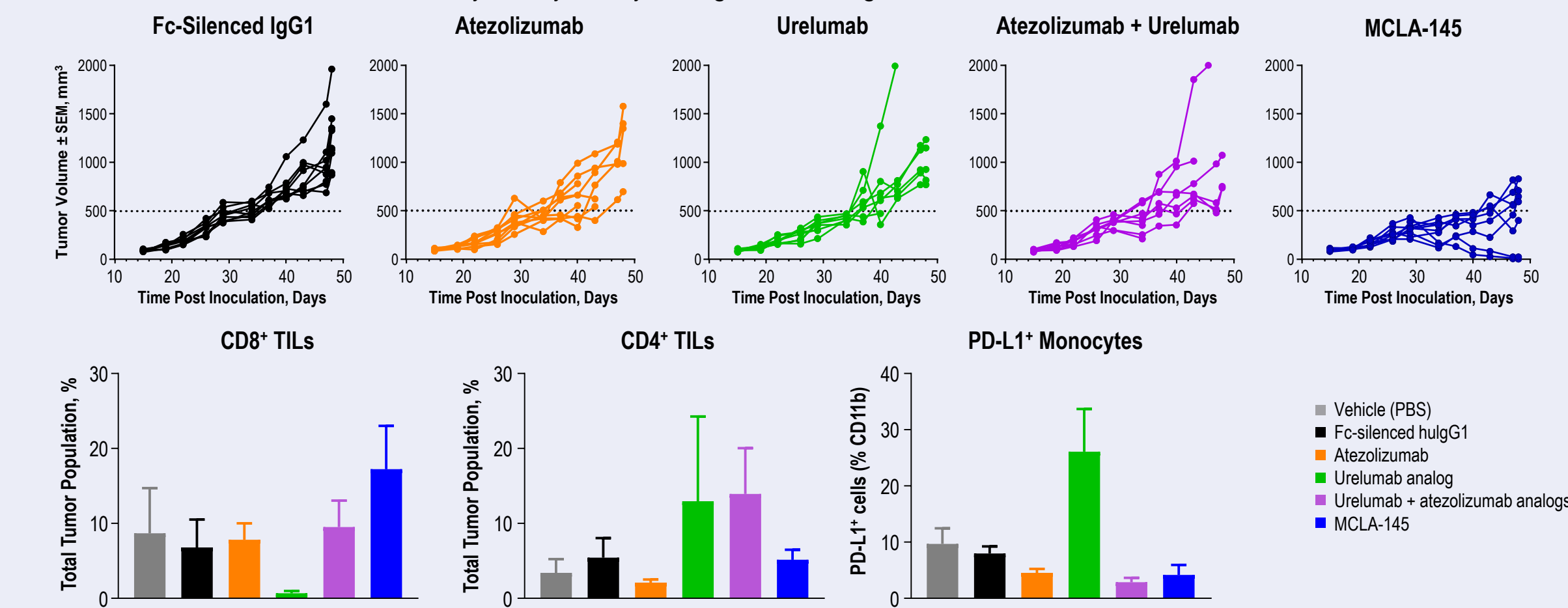


## Activity of MCLA-145 in Ex Vivo Human Primary Tumor Samples



## Antitumor Activity of MCLA-145 in Humanized MDA-MB-231 Model

- MCLA-145 enhances the antitumor activity of human CD34<sup>+</sup> cells engrafted in NSG mice with MDA-MB-231 tumors. MCLA-145, atezolizumab, and urelumab analog were given intraperitoneally at the dose of 5 mg/kg once every 5 days for a period of 31 days
- Human CD34<sup>+</sup> engrafted NSG mice bearing MDA-MB-231 tumors had increased total CD8<sup>+</sup> tumor infiltrating leukocytes in response to MCLA-145 treatment as measured by flow cytometry. No significant changes were observed for CD4<sup>+</sup> or PD-L1<sup>+</sup> cells



## Conclusions

- MCLA-145 is an Fc-silenced Biclonic<sup>®</sup> that engages human CD137 and PD-L1
- MCLA-145 induces CD137 signaling provided PD-L1 is present in its environment
- MCLA-145 induces cytokine production from T cells in ex vivo primary human tumors cells
- MCLA-145 demonstrates antitumor activity in humanized mouse tumor models
- The unique binding properties of MCLA-145 may result in an increased therapeutic window by specifically activating CD137 expressing cells in the tumor niche where PD-L1 is expressed, while simultaneously blocking inhibitory input from the PD-1/PD-L1 axis

## Disclosures

Patrick Mayes, Steve Wang, Thomas Condamine, Ashwini Kulkarni, Yao-bin Liu, Arpita Mondal, Leslie Hall, Peggy Scherle, Gregory Hollis, Reid Huber: Employment and stock ownership – Incyte Corporation. Paul Tacken, Pieter Fokko van Loo, Hans van der Maaden, Eric Rovers, Steef Engels, Floris Franssen, Mark Throsby, Cecile Geuijen: Employment and stock ownership – Merus NV. Edmund Moon, Steven Albelda: Received research funding – Incyte Corporation. Soyeon Kim, Marina Martinez, Shaun O'Brien: Nothing to disclose.

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