not α PD-L1 responsiveness for orthotopic BC treatment. Neither agent alone treated lung metastatic MB49 or MBT-2 but the drug combination improved survival in both tumor models. Combination treatment effects in lungs were distinct from bladder, requiring CD8+ T and NK cells, but not $\gamma\delta$ T cells.

Conclusions BC immunotherapy effects differ by anatomic compartment and use distinct mechanisms to treat primary and metastatic BC. CD122-directed IL-2 is a promising BC immunotherapy strategy, and IL-2c is a candidate mediator through innate immune effects. α PD-L1 could improve IL-2c efficacy by engagement of adaptive immune responses including to improve metastatic disease treatment efficacy.

Ethics Approval All procedures involving animals in this study were approved by the UT Health San Antonio Institutional Animal Care and Use Committee (IACUC) and conducted in accordance with UT Health San Antonio Department of Laboratory Animal Resources standards.

REFERENCES

- Shah AY, Gao J, Siefker-Radtke AO. Five new therapies or just one new treatment? A critical look at immune checkpoint inhibition in urothelial cancer: Future Medicine, 2017.
- Arenas-Ramirez N, Zou C, Popp S, et al. Improved cancer immunotherapy by a CD25-mimobody conferring selectivity to human interleukin-2. *Science translational medicine* 2016;**8**(367):367ra166-367ra166.

<http://dx.doi.org/10.1136/jitc-2020-SITC2020.0719>

720

TARGETING MARCO AND IL-37R ON ANTI-INFLAMMATORY MACROPHAGES IN LUNG CANCER BLOCKS REGULATORY T CELLS AND SHIFT BALANCE TO SUPPORT CYTOTOXIC LYMPHOCYTE FUNCTION

¹Linnéa La Fleur, ²Johan Botling, ¹Fei He, ¹Catarina Pelicano, ¹Giorgia Palano, ²Artur Mezheyski, ²Patrick Micke, ³Jeffrey Ravetch, ¹Mikael Karlsson, ¹Dhifaf Sarhan*. ¹Karolinska Institutet, Stockholm, Sweden; ²Uppsala University, Uppsala, Sweden; ³Rockefeller, New York, NY, USA

Background The progression and metastatic capacity of solid tumors are strongly influenced by immune cells in the tumor microenvironment (TME). In non-small cell lung cancer (NSCLC) accumulation of anti-inflammatory tumor-associated macrophages (TAMs) is associated with worse clinical outcome and resistance to therapy. Numerous clinical trials aiming to recover T cell anti-tumor activity have been failing due to the persistence immune suppression in TME. Thus, there is a clinical need for alternative treatments targeting the suppressive function of the TME. We have previously shown that antibodies targeting the scavenger receptor MARCO reprograms the pro-tumoral TAMs in murine cancer models. Here, we investigated the immune landscape of NSCLC in the presence of MARCO expressing TAMs. We tested targeting MARCO or the tumor mechanisms inducing MARCO on human TAMs and hypothesized that targeting these mechanisms will remodel the suppressive environment and relive the anti-tumor responses to increase the efficacy of immunotherapy.

Methods To test our hypothesis, we first investigated the immune landscape of NSCLC in the presence of pro-tumoral MARCO+TAMs compared with tumors infiltrated by MARCO-TAMs. We next used RNAseq to analyze differential gene expression in NSCLC tumors infiltrated by MARCO positive or negative macrophages. In vitro, cytokine differentiated macrophages alternatively cultured with lung cancer cell lines were co-cultured with Natural Killer (NK) cells and T cells to mimic their interaction in the TME. Later, macrophages were

treated with targeting antibodies and their phenotype and function were examined prior and following interaction with other immune cells.

Results We found that MARCO expressing TAM numbers correlated with increased occurrence of regulatory T cell and effector T cells and decreased NK cells in NSCLC infiltrated by MARCO+TAMs. Furthermore, transcriptomic data from the tumors uncovered a correlation between MARCO expression and the anti-inflammatory cytokine IL-37. Studies in vitro subsequently showed that lung cancer cells polarized macrophages to express MARCO and gain an anti-inflammatory phenotype through the release of IL-37. These human MARCO expressing TAMs blocked cytotoxic T cell and NK cell activation, inhibiting their proliferation, cytokine production and tumor killing capacity. Mechanistically, MARCO+macrophages enhanced regulatory T (Treg) cell proliferation and IL-10 production and diminished CD8 T cell activities. Targeting MARCO or IL-37 receptor (IL-37R) repolarized TAMs resulted in recovered cytolytic activity and anti-tumoral capacity of NK cells and T cells.

Conclusions In summary, our data demonstrate a novel immune therapeutic approach targeting human TAM immune suppression of NK and T cell anti-tumor activities and remodel immune suppression.

Ethics Approval The study was approved by Institutional Ethics Board, approval number Dnr 2013.977-31.1.

<http://dx.doi.org/10.1136/jitc-2020-SITC2020.0720>

721

AT1412, A PATIENT-DERIVED CD9 ANTIBODY IN PRECLINICAL DEVELOPMENT PROMOTING TUMOR IMMUNE INFILTRATION AND INDUCING TUMOR REJECTION

¹Remko Schotte*, ¹Julien Villaudy, ¹Martijn Kedde, ¹Wouter Pos, ¹Daniel Go, ¹Christien Fatmawati, ¹Gemma Moiset, ¹Etsuko Yasuda, ¹Madalina Cercel, ¹Esmay Franklin, ¹Susan van Hal, ¹Pauline van Helden, ²Els Verdegaaal, ²Sjoerd van der Burg, ¹Hergen Spits, ¹Hans van Eenennaam. ¹AIMM Therapeutics, Amsterdam, Netherlands; ²Leiden University Medical Center, Leiden, Netherlands

Background Adaptive immunity to cancer cells forms a crucial part of cancer immunotherapy. Recently, the importance of tumor B-cell signatures were shown to correlate with melanoma survival. We investigated whether tumor-targeting antibodies could be isolated from a patient that cured (now 13 years tumor-free) metastatic melanoma following adoptive transfer of ex vivo expanded autologous T cells.

Methods Patient's peripheral blood B cells were isolated and tested for the presence of tumor-reactive B cells using AIMM's immortalisation technology. Antibody AT1412 was identified by virtue of its differential binding to melanoma cells as compared to healthy melanocytes. AT1412 binds the tetraspanin CD9, a broadly expressed protein involved in multiple cellular activities in cancer and induces ADCC and ADAP by effector cells.

Results Spontaneous immune rejection of tumors was observed in human immune system (HIS) mouse models implanted with CD9 genetically-disrupted A375 melanoma (A375-CD9KO) tumor cells, while A375wt cells were not cleared. Most notably, no tumor rejection of A375-CD9KO tumors was observed in NSG mice, indicating that blockade of CD9 makes tumor cells susceptible to immune rejection. CD9 has been described to regulate integrin signaling, e.g. LFA-1, VLA-4, VCAM-1 and ICAM-1. AT1412 was shown to modulate CD9 function