pembrolizumab therapy and were correlated with response. Effector-type CNs enriched in tumor-infiltrating CD4+ T cells and dendritic cells were significantly increased after treatment in responders. In contrast, a regulatory T cell-enriched CN was significantly increased in non-responders before and after therapy. Furthermore, a spatial signature of cell-cell distances between tumor cells and effector/regulatory immune cells predicted therapy outcome. In addition, CIBERSORTx analysis revealed that tumor cells in responders, but not in non-responders, increased their expression of immune-activating genes.

Conclusions High-dimensional spatial analysis of CTCL tumors revealed a pre-existing immunosuppressive state in pembrolizumab non-responders. Thorough analysis of the TME therefore enables the discovery of novel spatial biomarkers in a concept that accounts for both cell type information and higher-order tumor architecture. Combining highly multiplexed microscopy with CIBERSORTx allows for the discovery of novel, predictive spatial biomarkers of immunotherapy response and will pave the way for future studies that functionally address these cell types and their interactions.

Disclosure Information C.M. Schürch: F. Consultant/Advisory Board; Modest; Enable Medicine, LLC. D.J. Phillips: None. M. Matusiak: None. B. Rivero Gutierrez: None. S.S. Bhate: None. G.L. Barlow: None. M.S. Khodadoust: B. Research Grant (principal investigator, collaborator or consultant and pending grants as well as grants already received); Significant; Corvus Pharmaceuticals. R. West: None. Y.H. Kim: B. Research Grant (principal investigator, collaborator or consultant and pending grants as well as grants already received); Significant; Merck, Horizon, Soligenix, miRagen, Forty Seven Inc., Neumedicine, Trillium, Galderma, Elorac. D. Speakers Bureau/Honoraria (speakers bureau, symposia, and expert witness); Significant; Innate Pharma, Eisai, Kyowa Hakko Kirin, Takeda, Seattle Genetics, Medivir, Portola Pharmaceuticals, Corvus Pharmaceuticals. G.P. Nolan: E. Ownership Interest (stock, stock options, patent or other intellectual property); Significant; Akoya Biosciences. F. Consultant/Advisory Board; Significant; Akoya Biosciences.

On Demand Talk: 'Lost in Translation'

04 MECHANISMS OF LUNG CANCER HYPER-PROGRESSION PROMOTED BY PD-1 IMMUNE CHECKPOINT BLOCKADE

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10.1136/jitc-2020-ITOC7.9

Background Immune checkpoint blockade (ICB) with antibodies against PD-1 or PD-L1 may provide therapeutic benefits in patients with non-small cell lung cancer (NSCLC). However, most tumours are resistant and cases of disease hyper-progression have also been reported.

Materials and Methods Genetically engineered mouse models of Kras^{G12D}p53^{null} NSCLC were treated with cisplatin along with antibodies against angiopoietin-2/VEGFA, PD-1 and CSF1R. Tumour growth was monitored by micro-computed tomography and the tumour vasculature and immune cell infiltrates were assessed by immunofluorescence staining and flow cytometry.

Results Combined angiopoietin-2/VEGFA blockade by a bispecific antibody (A2V) modulated the vasculature and abated

immunosuppressive macrophages while increasing CD8⁺ effector T cells in the tumours, achieving disease stabilization comparable or superior to cisplatin-based chemotherapy. However, these immunological responses were unexpectedly limited by the addition of a PD-1 antibody, which paradoxically enhanced progression of a fraction of the tumours through a mechanism involving regulatory T cells and macrophages. Elimination of tumour-associated macrophages with a CSF1R-blocking antibody induced NSCLC regression in combination with PD-1 blockade and cisplatin.

Conclusions The immune cell composition of the tumour determines the outcome of PD-1 blockade. In NSCLC, high infiltration of regulatory T cells and immunosuppressive macrophages may account for tumour hyper-progression upon ICB.

Disclosure Information A. Martinez-Usatorre: None. E. Kadioglu: None. C. Cianciaruso: None. B. Torchia: None. J. Faget: None. E. Meylan: None. M. Schmittnaegel: None. I. Keklikoglou: None. M. De Palma: None.

On Demand Talk: Young Researcher Session

05 DECONSTRUCTION OF HAMPERED DENDRITIC CELL DEVELOPMENT BY MICRO-ENVIRONMENTAL CROSSTALK IN AN ORGANOTYPIC HUMAN MELANOMA-IN-SKIN MODEL

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10.1136/jitc-2020-ITOC7.10

Background Immune suppressive conditions in the melanoma tumor microenvironment (TME) block dendritic cell (DC) development and lead to the accumulation of M2-like macrophages and myeloid-derived suppressor cells (MDSCs). This will effectively hamper T cell priming, recruitment, and effector functions, and so interfere with the efficacy of immunotherapy. Targeting tumor-mediated myeloid suppression represents an interesting therapeutic option to promote the immune attack on tumors. The preclinical human models currently used to study myeloid suppression often fail to reflect the complexity of the TME.

Materials and Methods To study the cross-talk between melanoma and stroma cells and assess its effect on DC differentiation, we therefore established an *in vitro* three-dimensional (3D) reconstructed organotypic human melanoma-in-skin (Mel-RhS) model, allowing the monitoring of tumor growth and progression for up to six weeks.

Results Significantly higher levels of immune suppressive cytokines (IL-10, M-CSF, VEGF, TGF-beta) were detected in the melanoma model, constructed with the BRAF- and PTEN-mutated SK-MEL-28 cell line, as compared to its control (without melanoma cells). Indeed, Mel-RhS culture supernatants interfered with monocyte-to-DC differentiation, leading to the development of M2-like macrophages with a distinct phenotype (CD14⁺CD11a⁺BDCA3⁺CD163⁺CD16⁺PDL1⁺PDL2⁺), as established by polychromatic flowcytometry. Correlation matrix heatmap analysis identified IL-10, TGF-beta and M-