performed a systematic review and meta-analysis of published articles evaluating the effects of overweight/obesity on survival and immune-related adverse events (irAEs).

Materials and Methods In analogy to Cochrane recommendations, systematic literature searches included all published articles in PubMed until February 2021 with key terms ‘obesity’ and ‘overweight’ and ICI treatment irrespective of cancer entity and ICI used. Further selection criteria for meta-analysis included WHO cut-offs for overweight/obesity. For the random effects meta-analysis, we used Hazard Ratios (HR) for overall and progression-free survival (OS, PFS) and Odds Ratios (OR) for occurrence of irAEs with corresponding 95% confidence intervals (95%CI), respectively.

Results A total of 30 studies (12,895 patients, 38% female) selected for meta-analysis revealed a superior survival of overweight/obese patients (PFS: HR 0.9, 95%CI 0.77-1.04, $p = 0.11$; OS: 0.74, 95%CI 0.63-0.92, $p = 0.0005$) compared to normal weight patients. In subgroup analyses based on sex, overweight/obese male patients showed increased survival (PFS: HR 0.79, 95%CI 0.63-1.00, $p = 0.05$; OS: 0.71, 95%CI 0.58-0.86, $p = 0.0005$), whereas overweight/obese female patients had similar survival probabilities compared to their normal weight counterparts (PFS: HR 1.01, 95%CI 0.69-1.47, $p = 0.96$; OS: HR 0.73, 95%CI 0.48-1.10, $p = 0.13$). Underweight patients showed inferior survival (PFS: HR 1.48, 95%CI 1.07-2.04, $p = 0.02$; OS: HR 1.86, 95%CI 1.13-3.04, $p = 0.01$). In addition, overweight/obese patients had a higher risk of developing irAEs with grade ≥ 3 (OR 1.91, 95%CI 1.18-3.10, $p = 0.008$).

Conclusions Our meta-analysis revealed that overweight/obesity is a beneficial factor for PFS and OS in a mixed cohort of cancer patients undergoing ICI treatment accompanied by an increased risk of severe irAEs. The differences between overweight/obese males and overweight/obese females might point to sex specific adipose distribution patterns and interactions of sex steroids on a molecular level. A significant number of studies included underweight patients into normal weight control groups which led to a compromised interpretation of the data and should be addressed in future studies.

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P01.07

DEPLETION OF CD206^{HIGH} TUMOUR-ASSOCIATED MACROPHAGES USING A NANOCONJUGATE LIMITS TUMOUR BURDEN & DISSEMINATION IN METASTATIC TRIPLE NEGATIVE BREAST CANCER IN MICE

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Background Anti-inflammatory (M2) tumour-associated macrophages (TAMs) exert protumoural roles through angiogenesis, immunosuppression and resistance to therapies.¹ M2 TAMs express the mannose receptor, CD206,² excellent marker for targeted therapies. We have previously identified a peptide called mUNO² that specifically binds to CD206 on M2 TAMs. Aiming to dissect the role of CD206^{high} M2 TAMs in the tumour progression and immunosuppression, we depleted them using an mUNO and doxorubicin (Adriamycin®)-containing polymer-drug nanoconjugate (St-PGA-DOX-mUNO, ‘Oxi-mUNO’) where the polymer backbone is branched polyglutamic acid (St-PGA).³

Materials and Methods We compared OximUNO with free DOX and the untargeted nanoconjugate St-PGA-DOX. To study the in vitro cytotoxicity of the nanoconjugates, we used M2 and M1 skewed macrophages derived from human blood buffy coat. To study the in vivo homing of nanoconjugates we used an orthotopic triple negative breast cancer (TNBC, 4T1 cells) model and a TNBC experimental metastases model in immunocompetent mice. For in vivo therapeutic efficacy studies, we used orthotopic and experimental metastases models of TNBC, and administered the compounds intraperitoneally (i. p.).

Results In vitro, OximUNO showed 39% higher toxicity to the primary human M2 macrophages than St-PGA-DOX, and 31% lower toxicity to the M1 macrophages than St-PGA-DOX. In vivo, OximUNO showed no change in creatinine or alanine aminotransferase values, indicating no toxic effects to the kidneys or liver. Compared to control St-PGA, i.p.-administered St-PGA-mUNO, showed improved homing to M2 TAMs in both orthotopic and experimental metastases models with low accumulation in the liver. In the orthotopic treatment study, only OximUNO significantly reduced the tumour volume and showed 56% and 38% less lung metastases than DOX and St-PGA-DOX, respectively. Additionally, DOX and St-PGA-DOX produced a significant bodyweight loss whereas OximUNO did not. Importantly, OximUNO treatment resulted in 2-5-fold increase in the ratio of CD8⁺/FOXP3⁺ expression, suggesting a shift in the immune landscape towards an immunostimulatory profile. In the experimental metastases model, OximUNO monotherapy resulted in the highest reduction of lung metastases, and this effect correlated with a significant reduction in CD206^{high} M2 TAMs; whereas no significant effect on M2 TAMs population was observed with DOX or untargeted nanoconjugate.

Conclusions Our data suggests that the elimination of CD206^{high} M2 TAMs with OximUNO suppresses spontaneous and experimental metastases in safe manner, shifts immune landscape towards immunostimulatory and could therefore be a potential treatment option for TNBC patients.

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P01.08 SARCOPENIA AS BIOMARKER FOR IMMUNOTHERAPY OUTCOMES AND IMMUNE-RELATED ADVERSE EVENTS – A SYSTEMATIC REVIEW AND META-ANALYSIS

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Background Sarcopenia is an established risk factor for oncologic treatments like surgical interventions and conventional chemotherapy. However, the impact of sarcopenia on treatment and immune-related adverse events (irAEs) of cancer patients treated with immune checkpoint inhibitors (ICIs) continues to be debated. Therefore, we performed a systematic review and meta-analysis of all published articles evaluating the effects of sarcopenia on survival outcomes and irAEs of patients undergoing ICI treatment.

Materials and Methods In analogy to the Cochrane guidelines for systematic reviews, we performed a systematic literature search including all published articles in PubMed until February 2021 for the key terms ‘sarcopenia’ or ‘sarcopenic obesity’ in combination with several terms for ICI treatments, irrespective of cancer entity and ICI used. Further selection criteria for meta-analysis included defined cut-offs for sarcopenia. Reported outcomes included progression-free survival (PFS), overall survival (OS) and the frequency of irAEs. For the random effects meta-analysis, we used Hazard Ratios (HR) for OS and PFS and Odds Ratios (OR) for occurrence of irAEs with corresponding 95% confidence intervals (95%CI), respectively.

Results A total of 15 studies with 1,428 patients were selected to be eligible for meta-analysis. To evaluate muscle mass, all studies used CT-derived body composition parameters at the third lumbar vertebrae level and defined sarcopenia by using skeletal muscle index (SMI), psoas muscle index (PMI) or skeletal muscle density (SMD). Sarcopenic patients showed an inferior survival compared to non-sarcopenic patients with a combined HR for PFS with 1.53 (95%CI 1.23-1.91, $p = 0.0001$) and for OS with 1.6 (95% CI 1.23-2.09, $p = 0.0005$). Frequency of irAEs did not differ between sarcopenic and non-sarcopenic patients regardless of irAE grade (irAEs of grade ≥ 3 : OR 1.14, 95%CI 0.65-2.01, $p = 0.64$, irAEs of any grade: OR 0.96, 95%CI 0.65-1.42, $p = 0.85$).

Conclusions This is the first meta-analysis that assessed sarcopenia in a mixed cohort of cancer patients. It revealed that sarcopenia is an adverse risk factor for survival of patients undergoing ICI treatment without affecting the risk of developing irAEs. Future studies may address sarcopenia as a patient-derived risk factor emphasizing the importance of nutrition and physical activity interventions.

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P02 Tumor microenvironment and microbiome in Immunotherapy

P02.01 T- AND B-CELL ABUNDANCE ARE REMARKABLY REDUCED IN THE IMMUNE MICROENVIRONMENT OF POST-TRANSPLANT MALIGNANCIES

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Background Immunosuppressive medication is mandatory in the majority of solid organ transplant recipients to reduce the risk of allograft rejection. An increased risk to develop cancer is a negative side effect of long-term immunosuppression and impaired cancer immunosurveillance is assumed as underlying mechanism. However, the impact of immunosuppression on the tumor immune microenvironment (TME) is poorly understood. In this study we aimed to elucidate differences between immune infiltrates of post-transplant malignancies and cancer of non-immunosuppressed patients.

Materials and Methods 117 resected tumor samples of 80 organ transplant (kidney, heart, lung and liver) recipients were included. Immunohistochemistry and digital image analysis of whole section slides was used to quantify T- (CD3, CD8) and B-cell (CD20) abundance in the TME of 14 different cancer types. These data were used to calculate the Immune-score and to quantify tertiary lymphoid structures in the TME. Expression of Human-Leucocyte-Antigen-I (HLA-I) and programmed cell death ligand 1 (PD-L1) were analyzed in tissue microarrays. Clinical parameters were included in statistical analyses.

Results The increased risk of cancer in organ transplant recipients was reflected by a remarkably reduced immune infiltrate in the central region (CT) and the surrounding tissue (invasive margin, IM) of cancer areas. T cell abundance was decreased in IM and CT of skin (814 vs. 1440 CD3⁺ cells/mm², $p < 0.01$) and non-skin tumors (479 vs. 781 CD3⁺ cells/mm², $p < 0.01$), when compared to non-immunosuppressed controls. These differences were more pronounced in the IM than in the CT and larger when comparing abundance of CD8⁺ T cells. The Immune-score integrating results from CT and IM was also decreased in transplant recipients. Similar to the results observed for T cells, B cell abundance and density of tertiary lymphoid structures were lower in cancer samples of transplant recipients. Decreased expression of HLA-I was more common in transplant recipients whereas the fraction of samples with PD-L1 expression was higher in controls.

Conclusions Our study demonstrates that post-transplant malignancies show a low immune infiltrate and supports the hypothesis of reduced anti-tumor immune response as an important mechanism underlying increased risk of cancer in organ transplant recipients. Optimized immunosuppressive protocols may be able to reduce cancer incidence and cancer therapies need to consider the distinct immune microenvironment of post-transplant malignancies.