Results Compared to monotherapies, combined Gvax/ α CD25 significantly delayed tumour growth and prolonged survival, in association with enhanced infiltration of T cells with an activated phenotype. Approximately 50% of mice achieved partial response with relapse at day 35–45 post tumor injection. To characterize immune evolution prior to relapse, we analysed stable, partially responding tumors and paired draining lymph nodes (DLNs). Over time, activated PD-1+ICOS+TCF7- T cells with an effector memory (CD44+CD62L-) phenotype fell from 30% to 10% whilst resting, TCF7+ early differentiated cells rose in abundance towards levels seen in untreated tumors. Abundance of Ki67-, resting Tregs also recovered. Similar results were obtained in analysis of DLNs.

Conclusions Combined Treg depletion/whole tumor vaccination therapy is effective in a poorly infiltrated B16 melanoma model. Combined treatment promotes T cell infiltration and activation. In mice achieving a partial response, treatment effects on the immune landscape were observed to decay over time suggesting a return to immune equilibrium. Further studies to explore the mechanistic basis of this observation are underway.

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P03.24 CALRETICULIN EXPOSURE ON MALIGNANT BLASTS CORRELATES WITH IMPROVED NK CELL-MEDIATED CYTOTOXICITY IN AML PATIENTS

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In some settings, cancer cells responding to treatment undergo an immunogenic form of cell death that is associated with the abundant emission of danger signals in the form of damage-associated molecular patterns. Accumulating preclinical and clinical evidence indicates that danger signals play a crucial role in the (re-)activation of antitumor immune responses in vivo, thus having a major impact on patient prognosis. We have previously demonstrated that the presence of calreticulin on the surface of malignant blasts is a

positive prognostic biomarker for patients with acute myeloid leukemia (AML). Calreticulin exposure not only correlated with enhanced T-cell-dependent antitumor immunity in this setting but also affected the number of circulating natural killer (NK) cells upon restoration of normal hematopoiesis. Here, we report that calreticulin exposure on malignant blasts is associated with enhanced NK cell cytotoxic and secretory functions, both in AML patients and in vivo in mice. The ability of calreticulin to stimulate NK-cells relies on CD11c+CD14high cells that, upon exposure to CRT, express higher levels of IL-15R α , maturation markers (CD86 and HLA-DR) and CCR7. CRT exposure on malignant blasts also correlates with the upregulation of genes coding for type I interferon. This suggests that CD11c+CD14high cells have increased capacity to migrate to secondary lymphoid organs, where can efficiently deliver stimulatory signals (IL-15R α /IL-15) to NK cells. These findings delineate a multipronged, clinically relevant mechanism whereby surface-exposed calreticulin favors NK-cell activation in AML patients.

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P03.25 NEUTRALIZING EXTRACELLULAR CHP-1 IMPAIRS TUMOR GROWTH AND METASTASIS FORMATION

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Background Found in the extracellular compartment, Heat Shock Proteins (HSPs) are actively secreted proteins that modulate the tumor behavior. Extracellular HSPs play a unique role as extracellular chaperones and receptors-binding molecules, favoring the establishment and maintenance of different cancer hallmarks, including immune modulation and evasion. CHP-1, is a ubiquitously expressed protein with chaperone activity and its high expression correlates with high tumor grade and lymph node positivity in different breast and lung cancer subtypes. In addition, CHP-1 is actively and uncanonically secreted by cancer cells in the tumor microenvironment (TME).

Materials and Methods Sera cancer patients were analyzed for the presence of CHP-1. To assess the role of extracellular CHP-1 (eCHP-1) in the TME, in vitro experiments on different cell populations have been performed. To dissect the molecular mechanisms, through which eCHP-1 induces cancer progression, have been analyzed specific signaling pathways in cancer and immune cells. Immune cell composition in presence of eCHP-1 in tumors has been identified using flow-cytometry. The characterization of eCHP-1 inhibition as therapeutic approach has been conducted in breast and colon cancer pre-clinical models.

Results eCHP-1 activates an autocrine signaling through TLR2, TLR4 and LRP1, promoting tumor progression and metastasis formation in different pre-clinical models. Moreover, eCHP-1 can modulate the immune composition of the TME, making interesting the analysis of its inhibition in cancer immunotherapy.