A HIGH-THROUGHPUT IN SITU SCREEN TO IDENTIFY SYNERGISTIC COMBINATIONS OF IMMUNE-ONCOLOGY DRUGS WITH TARGETED AND CYTOTOXIC AGENTS IN A PATIENT-DERIVED HUMANIZED MOUSE MODEL OF RENAL CANCER

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Background Identifying how to optimally combine immunotherapies with other available anti-cancer therapies is a major challenge in oncology. A systematic method to screen many potential combination therapies ideally in vivo has remained elusive. We have utilized an implantable microdevice (IMD) performing cassette microdosing that measures intratumor drug responses and anti-tumor immunity for 20 agents in parallel. For each of the agents, local tumor response is measured by cyclical immunofluorescence for deep cellular response phenotyping. This approach is combined with systemic administration of checkpoint inhibitors to examine whether local immunogenic cell death (ICD) induced by a given drug microdose potentiates the immunotherapy's anti-tumor effect.

Methods The measurements were performed in a humanized mouse model of renal cancer, patient derived xenograft (PDX) RXF488. The PDX is derived from a 68 year old male patient suffering from clear cell renal carcinoma. RXF488 was implanted subcutaneously in 30 NSG mice. Animals were stratified into 6 groups with n= 4–6. Humanization was performed by the intravenous injection of 5x10e6 human peripheral blood mononuclear cells (PBMC) prior to the first treatment. Systemic anti-PD1 treatment was applied in the presence and absence of the microdevice loaded with eleven different drugs. Control groups received the microdevice in the presence or absence of PBMC. Beside the histological examination of the tumor tissue, flow cytometry (FC) was performed on bone marrow, spleen and tumor tissue to determine infiltration of human immune cells.

Results FC analyses revealed no influence of the treatment on the human immune cells in bone marrow and spleen. The anti-PD1 treatment induced an increase in huCD45+ cells specifically in the tumor tissue and a decrease of the CD4/CD8 ratio in these cells only 48h after treatment. Our combination screen identified LXH254, Sorafenib and Doxorubicin exhibiting the highest increase in apoptosis induction when combined with checkpoint inhibitors. The increased efficacy from immunotherapy administration coincided with increased induction of ICD. We were able to verify the results of the screening experiment in a conventional setting with systemic combination treatment in the same PDX model.

Conclusions Our results demonstrate that local tumor response signatures of ICD can be used to systemically identify synergistic combinations of a range of drugs with immunotherapy on a tumor specific basis. The approach may represent a new paradigm for efficient in vivo screening of novel combinations, particularly with combinations involving immunotherapies.

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