**Background**

Before adjuvant checkpoint inhibition the 5-year overall survival (OS) rate was poor (<50%) in high-risk stage III melanoma patients. Adjuvant CTLA-4 (ipilimumab, IPI) and PD-1 (nivolumab, NIVO, or pembrolizumab) blockade have been shown to improve relapse-free survival (RFS) and OS (latter only for IPI so far). Due to a broader immune activation neoadjuvant therapy with checkpoint inhibitors might be more effective than adjuvant, as suggested in preclinical experiments. The OpACIN trial compared neoadjuvant versus adjuvant IPI plus NIVO, while the subsequent OpACIN-neo trial tested three different dosing schedules of neoadjuvant IPI plus NIVO without adjuvant therapy. High pathologic response rates of 74–78% were induced by neoadjuvant IPI plus NIVO. Here, we present the 36- and 24-months RFS of the OpACIN and OpACIN-neo trial, respectively.

**Materials and Methods**

The phase 1b OpACIN trial included 20 stage IIIIB/IIIC melanoma patients, which were randomized to receive IPI 3 mg/kg plus NIVO 1 mg/kg either adjuvant 4 cycles or split 2 cycles neoadjuvant and 2 adjuvant. In the phase 2 OpACIN-neo trial, 86 patients were randomized to 2 cycles neoadjuvant treatment, either in arm A: 2x IPI 3 mg/kg plus NIVO 1 mg/kg q3w (n=30), arm B: 2x IPI 1 mg/kg plus NIVO 3 mg/kg q3w (n=30), or arm C: 2x IPI 3 mg/kg q3w followed immediately by 2x NIVO 3 mg/kg q3w (n=26). Pathologic response was defined as <50% viable tumor cells and in both trials centrally reviewed by a blinded pathologist. RFS rates were estimated using the Kaplan-Meier method.

**Results**

Only 1 of 71 (1.4%) patients with a pathologic response on neoadjuvant therapy had relapsed, versus 16 of 23 patients (69.6%) without a pathologic response, after a median follow-up of 36 months for the OpACIN and 24 months for the OpACIN-neo trial. In the OpACIN trial, the estimated 3-year RFS rate for the neoadjuvant arm was 80% (95% CI: 59%-100%) versus 60% (95% CI: 36%-100%) for the adjuvant arm. Median RFS was not reached for any of the arms within the OpACIN-neo trial. Estimated 24-months RFS rate was 84% for all patients (95% CI: 76%-92%); 90% for arm A (95% CI: 80%-100%), 78% for arm B (95% CI: 63%-96%) and 83% for arm C (95% CI: 70%-100%). Baseline interferon-γ gene expression score and tumor mutational burden predict response.

**Conclusions**

OpACIN for the first time showed a potential benefit of neoadjuvant IPI plus NIVO versus adjuvant immunotherapy, whereas the OpACIN-neo trial confirmed the high pathologic response rates that can be achieved by neoadjuvant IPI plus NIVO. Both trials show that pathologic response can function as a surrogate markers for RFS.

**Clinical trial information**

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**Disclosure Information**

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RIG-I ACTIVATION ENHANCES MELANOMA IMMUNOGENICITY AND IMPROVES ANTI-TUMOR T CELL RESPONSES IN COMBINATION WITH ANTI-PD-1 IMMUNE CHECKPOINT BLOCKING ANTIBODIES

1B Thier, 1L Such, 1M Schwamborn, 1A Sucker, 2C Coch, 2D Schadendorf, 1K Giewenk, 3M Trilling, 1F Zhao, 1A Paschen, 4D Schadendorf, 1Institute of Virology, University Hospital Essen, Essen, Germany; 2German Cancer Consortium (DKTK), Partner Site Essen/Düsseldorf, Essen, Germany; 3Institute of Clinical Chemistry and Clinical Pharmacology, University Hospital Bonn, Bonn, Germany; 4Institute of Virology, University Hospital Essen, Essen, Germany

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Background Clinical efficacy of immune checkpoint blocking (ICB) therapy critically relies on the killing of melanoma cells by CD8+ T cells, becoming activated upon recognition of tumor antigens presented by HLA class I (HLA-I) surface molecules. Patient-derived melanoma cells can escape cytotoxic T cell effector functions by loss of HLA-I surface expression due to the silencing of HLA-I antigen processing and presentation machinery (APM) genes.

Material and Methods Seeking for a strategy to restore HLA-I expression, we transfected melanoma cells obtained from distinct patient metastasis with synthetic short double stranded RNA (3pRNA), an activating ligand of the cytosolic innate pattern recognition receptor RIG-I. 3pRNA-transfected melanoma cells were analyzed for HLA-I surface expression by FACS analysis and gene expression of HLA-I APM components by qPCR. In vivo 3pRNA-transfected tumors were analyzed for HLA-I expression by immunohistochemistry staining. Furthermore, T cell activation after coinubcation with 3pRNA-transfected melanoma cells was determined by IFNγ-ELISpot assay. The effect of combined 3pRNA and blocking anti-PD-1 antibody treatment on T cell activation was measured by intracellular cytokine staining and FACS analysis.

Results Activation of RIG-I by 3pRNA increased the expression of HLA-I APM components and strongly enhanced recognition of melanoma cells by autologous CD8+ T cells. Based on these findings, we asked whether the combination of 3pRNA and blocking anti-PD-1 antibodies could improve anti-melanoma T cell responses in an anti-PD-1 non-responder patient model. Indeed, T cell activation by 3pRNA-transfected melanoma cells was significantly increased in the presence of anti-PD-1 antibodies. In line with the enhancement of anti-tumor T cell responses, we found an association of elevated RIG-I mRNA levels with prolonged patient survival in TCGA melanoma samples.

Conclusions In summary, this study demonstrates a beneficial effect of RIG-I activation on antigen presentation and T cell recognition of melanoma cells. Improved T cell responses by combined 3pRNA and anti-PD-1 treatment suggests that combinatorial therapy could be a strategy to overcome T cell resistance in melanoma.


On Demand Talks

On Demand Talks: Tumor Microenvironment

01 TUMOR LACTIC ACIDOSIS ALTERS DECISIVE T CELL ACTIVITIES

1Al Fischbeck, 1AN Mendler, 2M Balles, 3J Schwarz, 3R Zantl, 1E Noesner. 4Helmholtz Zentrum München, Immunonanlytics, Munich, Germany; 5IBIDI GmbH, Gräfelfing, Germany

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Background Adoptive T cell therapy is a promising treatment strategy for tumor patients. However, when entering the tumor microenvironment (TME), T cells lose their effector function showing reduced degranulation and cytokine secretion. Besides T cell inhibition through checkpoint pathways (i.e. PD-1/L1, CTLA-4), suppressor cells (i.e. TAM, Treg) and cytokines (i.e. IL-10, TGF, VEGF), various metabolites of the TME also counteract antitumoral activities. Among the latter, lactate and extracellular acidosis are byproducts of the cancer metabolism and commonly observed in high concentrations in