L3 UPDATE OF THE OPACIN AND OPACIN-NEO TRIALS: 36-MONTHS AND 24-MONTHS RELAPSE-FREE SURVIVAL AFTER (NEO)ADJUVANT IPILIMUMAB PLUS NIVOLUMAB IN MACROSCOPIC STAGE III MELANOMA PATIENTS

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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 IIIB/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.

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L4 SYNTHETIC AGONISTIC RECEPTOR-ACTIVATING BITES – A MODULAR PLATFORM FOR THE EFFICIENT TARGETING OF ACUTE MYELOID LEUKEMIA

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Background Targeted immunotherapies have shown limited success in the context of acute myeloid leukemia (AML). Due to the mutational landscape and heterogeneity attributed to this malignancy and toxicities associated with the targeting of myeloid lineage antigens, it has become apparent that a modular and controllable cell therapy approach with the potential

to target multiple antigens is required. We propose a controlled ACT approach, where T cells are armed with synthetic agonistic receptors (SARs) that are conditionally activated only in the presence of a target AML-associated antigen, and a cross-linking bispecific T cell engager (BiTE) specific for both (SAR) T cell and tumour cell.

Materials and Methods A SAR composed of an extracellular EGFRvIII, trans-membrane CD28, and intracellular CD28 and CD3z domains was fused via overlap-extension PCR cloning. T cells were retrovirally transduced to stably express our SAR construct. SAR-specific bispecific T cell engagers (BiTE) that target AML-associated antigens were designed and expressed in Expi293F^{TM}cells and purified by nickel affinity and size exclusion chromatography (SEC). We validated our approach in three human cancer models and patient-derived AML blasts expressing our AML-associated target antigen CD33.

Results CD33-EGFRvIII BiTE, monovalently selective for our SAR, induced conditional antigen-dependent activation, proliferation and differentiation of SAR-T cells. Further, SAR T cells bridged to their target cells by BiTE could form functional immunological synapses, resulting in efficient tumor cell lysis with specificity towards CD33-expressing AML cells. SAR.BiTE combination could also mediate specific cytotoxicity against patient-derived AML blasts whilst driving SAR T cell activation. *In vivo*, treatment with SAR.BiTE combination could efficiently eradicate leukemia and enhance survival in an AML xenograft model. Furthermore, we could show selective activation of SAR T cells, as well as a controllable reversibility of said activation upon depletion of the T cell engaging molecule.

Conclusions Here we apply the SAR x BiAb approach in efforts to deliver specific and conditional activation of agonistic receptor-transduced T cells, and targeted tumour cell lysis. The modularity of our platform will allow for a multi-targeting ACT approach with the potential to translate the ACT successes of B cell malignancies to AML. With a lack of truly specific AML antigens, it is invaluable that this approach possesses an intrinsic safety switch via its BiTE facet. Moreover, we are able to circumvent pan-T cell activation due to the specific targeting and activation of SAR T cells.

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L5 RIG-I ACTIVATION ENHANCES MELANOMA IMMUNOGENICITY AND IMPROVES ANTI-TUMOR T CELL RESPONSES IN COMBINATION WITH ANTI-PD-1 IMMUNE CHECKPOINT BLOCKING ANTIBODIES

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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 from 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 coincubation 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 combinational therapy could be a strategy to overcome T cell resistance in melanoma.

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On Demand Talks

On Demand Talks: Tumor Microenvironment

O1 TUMOR LACTIC ACIDOSIS ALTERS DECISIVE T CELL ACTIVITIES

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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, T_{reg}) 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