unchanged. Therefore, interruption of MERTK signaling on T cells has a specific effect on cell division rather than cytotoxic function on a cell by cell basis. This has potential ramifications on the use of MERTK inhibitors to treat tumors where the ability to form substantial cytotoxic T cell populations might be reduced. In addition, increased MERTK expression on central memory subsets during long term culture suggests this signaling pathway could be critical for generating memory pools of T cells and provide new avenues for the improvement of adoptive T cell therapy protocols.

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Disclosure Information R.M. Powell: None. M.J.W. Peeters: None. A. Rachbech: None. P.T. Straten: None.

P01.14 EXCESSIVE BIOLOGICAL AGEING OF CIRCULATING NEUTROPHILS IN CANCER PROMOTES TUMOR PROGRESSION

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10.1136/jitc-2020-ITOC7.27

Background Beyond their well-established role in host defense, neutrophils are increasingly recognized to contribute to the pathogenesis of malignant tumors. Recently, ageing of mature neutrophils in the systemic circulation has been identified to be critical for these immune cells to properly unfold their anti-infectious properties. The role of neutrophil ageing in cancer is still unknown.

Material and Methods Employing syngeneic mouse models of head and neck squamous cell carcinoma (cell line SCC VII) and breast cancer (cell line 4T1), cytokine expression (by multiplex ELISA), neutrophil trafficking (by multi-channel *in vivo* microscopy and flow cytometry), and neutrophil function (*in vitro* assays) were analyzed.

Results Here, we show that signals released during early tumor growth promote excessive biological ageing of circulating neutrophils as indicated by age-related changes in their molecular repertoire. These events facilitate the accumulation of these highly reactive immune cells in malignant lesions and endow them with potent pro-tumorigenic functions. In particular, excessively aged neutrophils release neutrophil elastase which, in turn, stimulates the proliferation of cancer cells. Counteracting accelerated biological ageing of circulating neutrophils by blocking the chemokine receptor CXCR2 effectively suppressed tumor growth.

Conclusions Our experimental data uncover a potent self-sustaining mechanism of malignant tumors in fostering pro-tumorigenic phenotypic and functional changes in circulating neutrophils, thus supporting tumor progression. Interference with this aberrant process might provide a novel, already pharmacologically targetable strategy for cancer therapy. *This study was supported by Deutsche Forschungsgemeinschaft (DFG), Sonderforschungsbereich (SFB) 914.*

Disclosure Information C.A. Reichel: None. L. Mittmann: None. J. Schaubächer: None. R. Hennel: None. G.

Zuchtriegel: None. M. Canis: None. O. Gires: None. F. Krombach: None. L. Holdt: None. S. Brandau: None. T. Vogl: None. K. Lauber: None. B. Uhl: None.

P01.15 PERSONALIZED COMBINATION OF NEOADJUVANT DOMATINOSTAT, NIVOLUMAB (NIVO) AND IPILIMUMAB (IPI) IN MACROSCOPIC STAGE III MELANOMA PATIENTS STRATIFIED ACCORDING TO INTERFERON-GAMMA (IFN-GAMMA) SIGNATURE – THE DONIMI STUDY

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10.1136/jitc-2020-ITOC7.28

Background The previous OpACIN and OpACIN-neo studies investigating neoadjuvant IPI plus NIVO have demonstrated high pathologic response rates (74–78%) and favorable long-term outcomes for patients (pts) with a pathological response; at 36 and 18 months follow up only 1/71 (1.4%) responders has relapsed. In contrast, pathological non-responders have a poor prognosis; 15/23 (65.2%) have relapsed so far. This emphasizes the need for baseline biomarkers predictive of non-response and new neoadjuvant treatment combinations for these pts. In our previous studies, baseline IFN- γ signature high pts were more likely to respond to IPI plus NIVO. The DONIMI study tests the combination of NIVO $\pm$ IPI combined with a class 1 histone deacetylase inhibitor, domatinostat (DOM), according to the pts IFN- γ signature. We have developed a neoadjuvant IFN- γ signature, based on the signature previously described by Ayers *et al.*, that will be used for the first time to classify pts in this prospective trial.

Trial design This two-center investigator-initiated phase 1b study aims to assess the safety and feasibility of neoadjuvant NIVO $\pm$ DOM $\pm$ IPI in 45 stage III melanoma pts with macroscopic de-novo or recurrent disease. IFN- γ signature high pts (n=20) will be randomized (stratified by center) to Arm A (2 cycles NIVO 240 mg q3wk) or Arm B (2 cycles NIVO 240 mg q3wk + DOM 200 mg twice daily (BID), d1-14, q3wk). IFN- γ signature low pts (n=25) will be randomized to Arm C (2 cycles NIVO 240 mg q3wk + DOM 200 mg BID, d1-14, q3wk) or Arm D (2 cycles NIVO 240 mg q3wk + IPI 80 mg q3wk + DOM 200 mg once daily (OD), d1-14, q3wk). Based on safety data of the first 5 pts in arm D, the remaining pts will be treated with either a higher dosing scheme (200 mg BID, d1-14, q3wks), a lower dosing scheme (100 mg OD, d1-14, q3wks) or the same dosing scheme (200 mg OD, d1-14, q3wks). The primary endpoint is safety and feasibility. A treatment arm will be declared as not feasible if 2/5 or 3/10 patients cannot adhere to the planned time of surgery (week 6 $\pm$ 1week) due to treatment-related adverse events. Biopsies (week 0, 3), blood samples (week 0, 3, 6, 12) and feces (week 0, 3, 6) will be collected for translational research. To date, 7 patients have been enrolled.

Clinical trial information NCT04133948

Disclosure Information I.L.M. Reijers: None. E.A. Rozeman: None. P. Dimitriadis: None. O. Krijgsman: C. Other Research Support (supplies, equipment, receipt of drugs or other in-kind support); Modest; BMS. L.J.W. Bosch: None. S. Cornelissen: None. J. Bouwman: None. J.M. Versluis: None. D.