Results In line with previous reports for CAR-T cells, dasatinib (a src inhibitor) was found to fully switch off TCB-induced T cell functionality as well as the other src inhibitors bosutinib and ponatinib. In contrast, temsirolimus, sirolimus and everolimus (mTOR inhibitors) and ruxolitinib, baricitinib, tofacitinib, and fedratinib (JAK1/2 inhibitors) were found to more potently prevent TCB-induced cytokine release without blocking TCB-mediated target cell killing.

Conclusions These results provide evidence that the mechanisms of TCB-dependent cytokine release and tumor cell killing can be uncoupled. The FDA-approved mTOR and JAK1/2 inhibitors could potentially be used to mitigate CRS whereas the Src inhibitor dasatinib could rather stand as a potential antidote for on-target off-tumor activity or high-grade CRS.

Disclosure Information G. Leclercq: A. Employment (full or part-time); Modest; Roche. E. Ownership Interest (stock, stock options, patent or other intellectual property); Modest; Roche. **H. Haegel:** A. Employment (full or part-time); Modest; Roche. E. Ownership Interest (stock, stock options, patent or other intellectual property); Modest; Roche. **A. Schneider:** A. Employment (full or part-time); Modest; Roche. **A. Giusti:** A. Employment (full or part-time); Modest; Roche. **V. Pulko:** A. Employment (full or part-time); Modest; Roche. **A. Toso:** A. Employment (full or part-time); Modest; Roche. **T. Zimmermann:** A. Employment (full or part-time); Modest; Roche. **L. Green:** A. Employment (full or part-time); Modest; Roche. **N. Steinhoff:** A. Employment (full or part-time); Modest; Roche. **J. Sam:** A. Employment (full or part-time); Modest; Roche. **M. Bacac:** A. Employment (full or part-time); Modest; Roche. E. Ownership Interest (stock, stock options, patent or other intellectual property); Modest; Roche. **P. Umaña:** A. Employment (full or part-time); Modest; Roche. E. Ownership Interest (stock, stock options, patent or other intellectual property); Modest; Roche. **C. Klein:** A. Employment (full or part-time); Modest; Roche. E. Ownership Interest (stock, stock options, patent or other intellectual property); Modest; Roche.

P09.02 EPIGENETIC MODULATION OF NEUROBLASTOMA ENHANCES T- AND NK CELL IMMUNOGENICITY VIA INDUCTION OF SURFACE EXPRESSION OF MHC CLASS I AND MICA/MICB

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10.1136/jitc-2021-ITOC8.52

Background Neuroblastoma (NBL) is the most common pediatric solid tumor and responsible for about 15% of all pediatric cancer deaths. The majority of high-risk (HR) patients suffers from relapse after intense therapy regimens, resulting in a 5-year survival rate of only 40%. Even though the potential of immune interference in HR-NBL is shown by the additive effect of anti-GD2 monoclonal antibody therapy to the treatment protocol, long-term follow-up studies reveal that the beneficial effect of immunotherapy diminishes over time. We hypothesize that this is a result of inadequate (adaptive) immune engagement caused by the extensive immunomodulatory capacity of HR-NBL and its microenvironment. One of the most remarkable immunomodulatory strategies of NBL tumors is the absence of MHC-I surface expression, thereby preventing cytotoxic T cell recognition and killing. MHC-I lacking cells are known to be subjected to NK cell mediated cytotoxicity, however, we have shown that NBL is able to evade this by temporary upregulating surface expression of MHC-I, thereby becoming temporarily more prone to T cell mediated cytotoxicity. The aim of this project is to identify pharmacological strategies to enhance adaptive immune activation and therewith immunogenicity of HR-NBL.

Materials and Methods FDA-approved drug libraries were screened to identify compounds enhancing MHC-I surface expression in NBL cell lines using high-throughput flow cytometry analyses optimized for adherent NBL cells. The effect of positive hits was subsequently confirmed in a panel of NBL patient-derived tumeroids. Alterations in the transcriptome and translatome upon incubation with compounds of interest were further studied to identify potential additional immunomodulatory effects in NBL. Ultimately, compound treated NBL cell lines and tumeroids were co-cultured with PRAME reactive tumor-specific T cells and healthy-donor NK cells to determine the *in vitro* effect on T- and NK cell cytotoxicity.

Results Drug library screening revealed MHC-I upregulation upon treatment of NBL cell lines and patient-derived tumeroids with multiple histon deacetylase inhibitors (HDACi). Further investigation of immunomodulatory effects of HDACi in NBL revealed enhanced expression of several additional players of the antigen presenting machinery, immunoproteasome expression, and MICA/MICB upregulation in NBL cells. We show that in untreated NBL cells, plasticity of MHC-I expression causes evasion of both NK- and T cell mediated cytotoxicity. Intriguingly, co-culture of NBL cells with tumor-specific T cells and healthy-donor NK cells upon treatment with the HDACi Entinostat resulted in enhanced *in vitro* T- and NK cell activation and cytotoxicity.

Conclusions We show pharmacological upregulation of MHC-I, other antigen presenting machinery players, and the NKG2D ligands MICA/MICB upon HDACi in HR-NBL. Pretreatment of NBL with HDACi resulted in enhanced *in vitro* T- and NK cell mediated cytotoxicity, substantiating HDACi as a potential strategy to improve adaptive immune engagement and therewith immunogenicity to aid NBL treatment.

This work was supported by the Villa Joep Foundation [IWOV-Actief.51391.180034].

Disclosure Information A.M. Cornel: None. **D.A.M.H. van den Beemt:** None. **E. Dunnebach:** None. **M.P. van Dierselhuis:** None. **S. Nierkens:** None.

P09.03 HYALURONIC ACID AS A NEW IMMUNOLOGIC ADJUVANT IN CANCER: DESIGN OF EFFECTIVE PREVENTIVE AND THERAPEUTIC VACCINATION STRATEGIES FOR HER2/NEU-POSITIVE BREAST TUMORS

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10.1136/jitc-2021-ITOC8.53

Background The use of proteins as immunogens is attractive for the development of vaccines, but requires efficient adjuvants to overcome their weak immunogenicity. Recently, we investigated the potential of the TLR2/4 agonist hyaluronan (HA) as an immunological adjuvant for protein-based vaccines.[1] [2] Conjugation of HA to antigens strongly increased