AN IMMUNOCYTOKINE WITH TARGET CELL-RESTRICTED IL-15 ACTIVITY FOR INDUCTION OF ANTI-TUMOR IMMUNITY AGAINST ACUTE MYELOID LEUKEMIA

Martina S Lutz*, Bastian Schmied, Fabian Riegg, Latifa Zekri, Melanie Märklin, Martin Pflügler, Gundram Jung, Helmut R Salih. Eberhard Karls University, Tuebingen, Baden-Wuerttemberg, Germany

**Background** Despite the significant progress achieved in cancer treatment by the use of antitumor antibodies, there remains an urgent need to optimize their therapeutic efficacy. We recently completed a phase I trial evaluating safety/tolerability and preliminary efficacy of an Fc-optimized FLT3/CD135 antibody (FLYSYN, NCT02789254) to induce NK cell anti-leukemia reactivity against AML cells. Besides by reinforcing the capability of antibodies to induce antibody-dependent cellular cytotoxicity (ADCC), NK cell immunity can be further increased using cytokines like IL-15. However, the application of clinically effective doses of IL-15 is hindered by significant side effects caused by nonspecific immune activation.

**Methods** We generated a modified immunocytokine (MIC) consisting of our Fc-optimized CD135 antibody fused to mutated IL-15 with abolished binding to IL-15 receptor alpha (MIC135). This abrogated binding allows to substitute the trans-presentation of IL-15, which physiologically is required to stimulate the IL-15 receptor beta/gamma on NK cells, by binding of the antibody part to CD135 on leukemic cells. The efficacy of our construct was evaluated in various in vitro assays using primary AML cells as targets.

**Results** Functional analysis revealed that MIC135 exhibited significantly greater induction of target-restricted NK cell anti-leukemia reactivity compared to the Fc-optimized FLYSYN mAb. Notably, in stark contrast to FLYSYN, MIC135 induced pronounced NK cell proliferation, and target cell killing was likewise clearly superior. Analyses regarding off-target toxicity confirmed that MIC135 exhibited target-antigen restricted efficacy, in contrast to anti-CD135 immunocytokines with wild-type IL-15 (IC135). MIC135 did not induce unwanted effects against healthy FLT3 expressing cells.

**Conclusions** MIC135 induces NK cell reactivity against leukemia cells in a target cell-restricted manner and exhibits superior efficacy compared to Fc-optimized antibodies, thus constituting a promising treatment option for AML.

**Ethics Approval** The studies involving human participants were reviewed and approved by IRB (ethics committee of the Faculty of Medicine of the Eberhard Karls Universität Tübingen) at the University Hospital Tübingen and was conducted in accordance with the Declaration of Helsinki; reference number 13/2007V.

Consent Human material was collected after obtaining informed consent. The patients/participants provided their written informed consent to participate in this study.

http://dx.doi.org/10.1136/jitc-2023-SITC2023.1365