Resistance to epidermal growth factor receptor (EGFR) targeting therapy of therapeutic antibodies like cetuximab and bevacizumab (CAPOX-B) (A). To evaluate the functional implications of patient NK cells, we exposed PBNK cells to a NK cell and cetuximab sensitive target (A431; EGFR**+**RASmut) to test natural cytotoxicity and ADCC (ET ratio 1:1:4, 4h, based on 7-AAD) (B). Natural cytotoxicity of CRC patient's NK cells were highly impaired, and ADCC was still maintained, apparent from their low degradation rates at baseline and post chemotherapy (one-way ANOVA *p<0.05, **p<0.01, ***p<0.005).

UCB-NK have superior cytotoxic efficacy than A-PBNK

CRC patient's NK cells are highly dysfunctional

Figure 2: Low prevalence and functionally impaired NK cells in CRC patients.

To address whether significant antitumor effect by UCB-NK can be translated into survival advantage in vivo, the mice were monitored for survival benefits. Robust growth and spread of SW480 cells resulted in death of all untreated control mice between 36 to 38 post tumor injection, CET as monotherapy demonstrated no increased efficacy as expected. However, treatment of mice with UCB-NK alone resulted in a significant prolongation in the life span (60 to 65 days post tumor injection), with no added benefit of CET, besides CD16 upregulation in vivo on UCB-NK. (Log rank Mantel-Cox test **p<0.01, ***p<0.005).

Conclusions and perspectives

- UCB-NK exhibit higher cytotoxic effects on CRC cells compared to A-PBNK
- UCB-NK successfully inhibit cancer growth and increase survival in RAS mutant cancer models.
- Our results provide a clear rationale to use UCB-NK for RAS wild type and RAS mutant colon cancer treatment.
- To start a clinical trial using UCB-NK in mCRC patients.
- To explore further opportunities to enhance CRC treatment combining UCB-NK with bispecific monoclonal antibodies.