NK cells are part of the innate immune system that are not antigen-specific, but can be redirected to targets of interest using multiple strategies. Advantages of NK cells over T cells include the use of allogeneic off-the-shelf products and lower risk of cytokine release syndrome. Numerous NK-specific immunotherapies are under development for the treatment of cancer, although none are yet FDA-approved. Here, we conducted a pan-cancer analysis of NK cell abundance in >90,000 tumor samples across 45 cancer types using the Caris Precision Oncology Allotest (POA) database. Features of prostate cancer (PCa, n=3365) and renal cell carcinoma (RCC, n=1106) were explored in depth.

**Background:**
NK cell fractions from 7-9% (medulloblastoma and gliomas) to 2% (thyroid and thymic cancers), with intermediate levels observed for PCa (4.6%) and RCC (3.1%). High (> median) NK cell fractions were associated with improved OS (hazard ratios, 0.28–0.84, p<0.05) for 28 of 45 cancer types, while 16 of 45 including PRAD and RCC (3.1%) had HRs <0.50 with 95% CI crossing 1.0. Improved OS was notable in PCa (HR 0.46, 95% CI 0.38–0.56, p<0.0001) and RCC (HR 0.52; 95% CI 0.39–0.70, p<0.0001) (Finotello, 2019). Real-world overall survival (OS) was determined from insurance claims, and Kaplan-Meier estimates were calculated. Statistical significance was determined using Chi- and Mann-Whitney U tests with corrections for multiple hypothesis testing where appropriate.

**Results:**
Median NK cell fractions ranged from 7-9% (medulloblastoma and gliomas) to 2% (thyroid and thymic cancers), with intermediate levels observed for PCa (4.6%) and RCC (3.1%). High (> median) NK cell fractions were associated with improved OS (hazard ratios, 0.28–0.84, p<0.05) for 28 of 45 cancer types, while 16 of 45 including PRAD and RCC (3.1%) had HRs <0.50 with 95% CI crossing 1.0. Improved OS was notable in PCa (HR 0.46, 95% CI 0.38–0.56, p<0.0001) and RCC (HR 0.52; 95% CI 0.39–0.70, p<0.0001) (Finotello, 2019). Real-world overall survival (OS) was determined from insurance claims, and Kaplan-Meier estimates were calculated. Statistical significance was determined using Chi- and Mann-Whitney U tests with corrections for multiple hypothesis testing where appropriate.

**Medians NK Cell Infiltration As a Percentage of Total Cells Across Human Cancers**

**High NK cell infiltration is associated with improved OS in numerous cancer types**

- **Figure 1.** NK cell fraction as a percentage of all cells calculated using quanTiseq for immune deconvolution using transcriptomic data. A total of 90,916 samples from 45 distinct tumor types were analyzed.

**Figure 2.** Association of overall survival (OS) in tumors with top 75th percentile NK cell infiltration (relative to all cancers) across 45 different tumor types. Dotted line represents Hazard Ratio of 1.0. Bottom-Box-Kaplan-Meier curves for prostate adenocarcinoma (PRAD) and renal cell carcinoma (RCC) demonstrate significant overall survival differences between top 25 percentile (red) and >75 percentile NK cell infiltration. *p <0.05, **p <0.01, ***p <0.001, ****p <0.0001

**Figure 3.** A/B-Biomarker and mutational frequency associated with <25 percentile and >75 percentile relative to PCa (A) and RCC (B) NK cell infiltration. Error bars represent 95% CI and *q-values. (**<0.0001, ***<0.001)

**Figure 4.** Tumor biopsy sample expression of NK cell-specific chemokines in PRAD and RCC relative to NK cell high versus low tumors. P<0.05 denoted by dotted line.

**Conclusions:**
- **High NK cell infiltration is associated with improved OS in numerous cancers.**
- These findings suggest broad deployment of NK engagers and CAR-NK.
- The positive correlation between NK cells and LAG3/TIGIT suggest that combination approaches may be warranted.
- These findings support the use of NK cells in situations where other immune therapies have proven to be ineffective.

**Acknowledgements:**
NAZ is supported by the Randy Shaver Prostate Cancer Foundation Young Investigators Award and a Department of Defense EIRA Award (W81XWH-22-1-0242).

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