2563: Pan-Cancer Analysis of Natural Killer (NK) Cell Infiltration in Human Malignancies: Molecular Features and Clinical Implications

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Background: 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 Alliance (POA) database. Features of prostate cancer (PCa, n=3365) and renal cell carcinoma (RCC, n=1106) were explored in depth.

Methods: DNA (targeted/whole-exome) and RNA (whole-transcriptome) sequencing was performed for patient tumors (N=90,916) submitted to Caris Life Sciences (Phoenix, AZ). NK cell fractions were inferred from RNA-seq data using quanTIseq (Finotello, 2019). Real-world overall survival (OS) was determined from insurance claims, and Kaplan-Meier estimates were calculated. Statistical significance was determined using X^2 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 low-grade glioma, GIST, and thyroid had HR <1.0 (0.264-0.997) 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). Unexpectedly, tumors with higher NK infiltrates were less frequently PD-L1+ (SP142) by IHC in PCa (2.8% vs 5.4%, p=0.08) and RCC (12.4% vs 30.8%, p<0.0001) (*i.e.* an inverse relationship), despite a lack of correlation of NK infiltration with dMMR/MSI status or tumor mutation burden (TMB) in both cancers. Conversely, increased NK infiltration was associated with a 1.4- to 2.1–fold increased mRNA expression of immunomodulatory receptors *LAG3* and *TIGIT* in both PCa (p<0.0001) and RCC (p<0.0001), but a 1.4–fold decrease in *B7-H3* in RCC (p<0.0001).

Conclusion: High NK cell infiltration is associated with improved OS in numerous cancer types, including many with inadequate therapeutic options. Our findings suggest broad deployment of NK engagers and CAR-NK products in a range of malignancies. The positive correlation between NK cells and LAG3/TIGIT suggest that combination approaches may be warranted. The inverse relationship between NK infiltrates and PD-L1, and lack of association with standard immune therapy markers (MSI status, TMB), indicates the potential use of NK cell approaches in situations where other immunotherapies are ineffective.

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

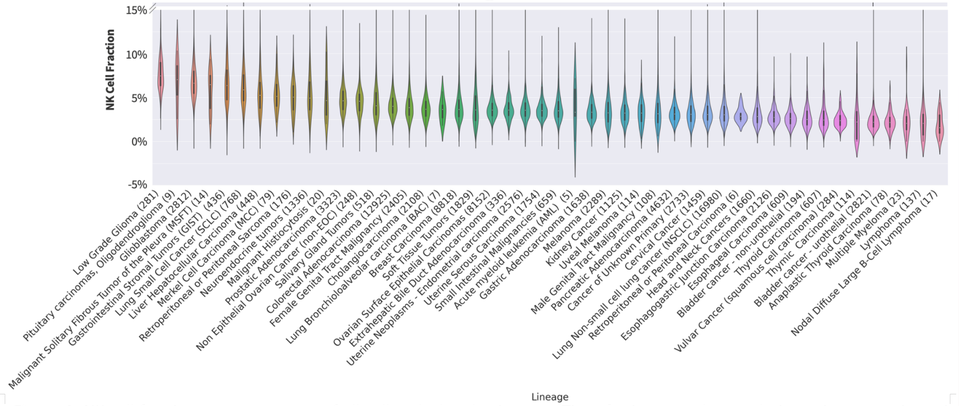
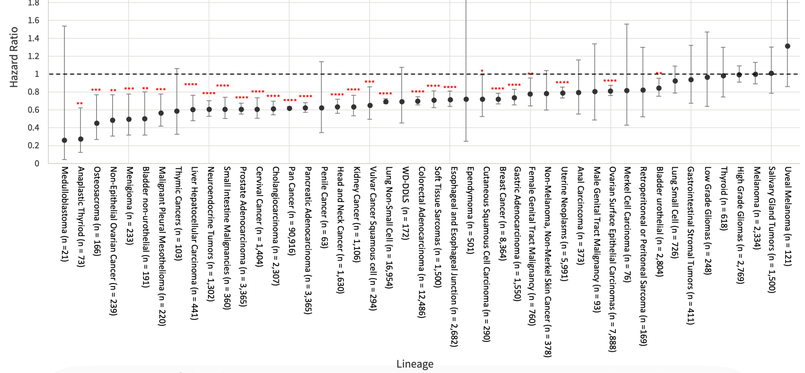


Figure 1. NK cell fraction as a percentage of all cells calculated using quanTiseq for immune deconvolution using transcriptomic data. A total of 90.916 samples from 45 distinct tumor types were analyzed.

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



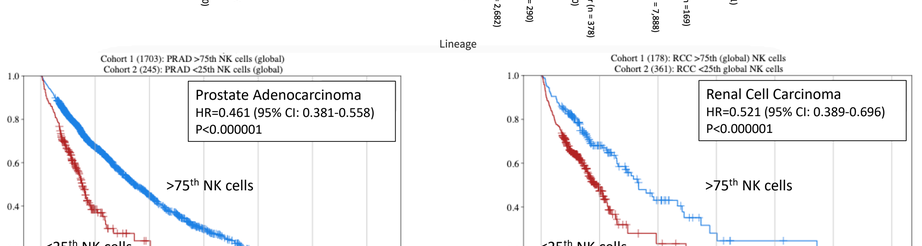


Figure 2. Top-Association of overall survival (OS) in tumors with top 75th percentile NK cell infiltration (relative to all cancers) across 45 different tumor types. Dotted line represents Hazard Ratio of 1.0. **Bottom**-Kaplan-Meier curves for prostate adenocarcinoma (PRAD) and renal cell carcinoma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

NK Cell Infiltration Association with Common Driver Mutations, Immune Subsets, and Immune Modulatory Receptors

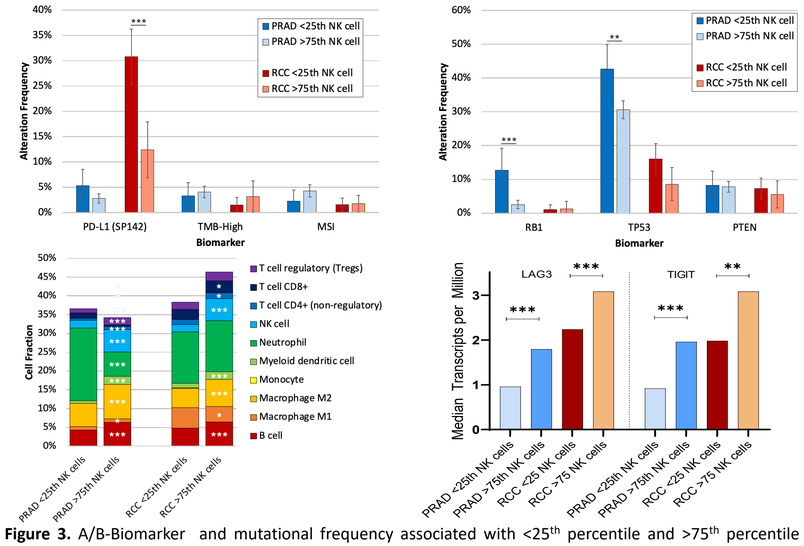


Figure 3. A/B-Biomarker and mutational frequency associated with <25th percentile and >75th percentile (relative to all cancers) NK cell infiltration in PRAD and RCC. Error bars represent 95% CI and *q-values. C-Immune cell deconvolution using quanTiseq demonstrates differences in the immune landscape in prostate adenocarcinoma and RCC when comparing <25th and >75th percentile NK cell infiltration groups. * p-values **D**-Association of NK cell infiltration with LAG3 and TIGIT in PRAD and RCC. * q-values (**<0.0001, *** 0.0)

Chemokine Associations with NK Cell Infiltration

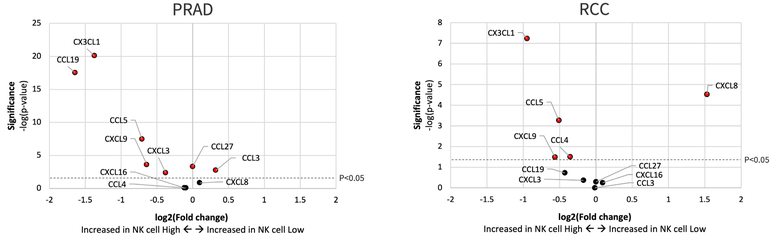


Figure 4. Tumor biopsy sample expression of NK cell-specific chemokines in PRAD and RCC relative to NK cell high versus low tumors. *P*<0.05 denoted by dotted line.

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.**