

Pelareorep induces expansion of mutant KRAS-specific TIL clones in the blood

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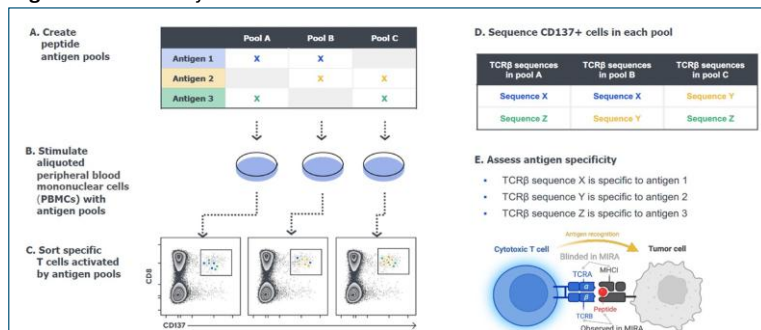
Background

Pelareorep (pela) is an intravenously delivered, genetically unmodified oncolytic reovirus that selectively infects cancer cells and is being developed as an immunotherapy for multiple cancers. Its double-stranded RNA (dsRNA) genome contributes to its ability to stimulate strong immune responses. We report here the analysis of tumor and blood samples from breast and pancreatic cancer patients that demonstrate a multi-step process of innate, virus, and tumor-specific immune activation culminating in the expansion of tumor-specific mutant KRAS (mKRAS) T cell clones that are associated with reductions in tumor volume.

Methods

Blood and tumor samples were obtained from patients in the AWARE-1 trial (breast cancer) and the GOBLET trial (pancreatic cancer [PDAC]). Tumor gene expression was assessed using RNA from formalin-fixed paraffin-embedded (FFPE) breast tumor samples collected at baseline, Day 3 and Day 21 of therapy. PDAC samples were analyzed by T cell receptor (TCR) expression (Adaptive Biotechnologies, Seattle, WA). KRAS specificity of selected T cell clones was determined by multiplexed identification of T-cell receptor antigen specificity (MIRA) assay (Figure 1).

Figure 1. MIRA assay

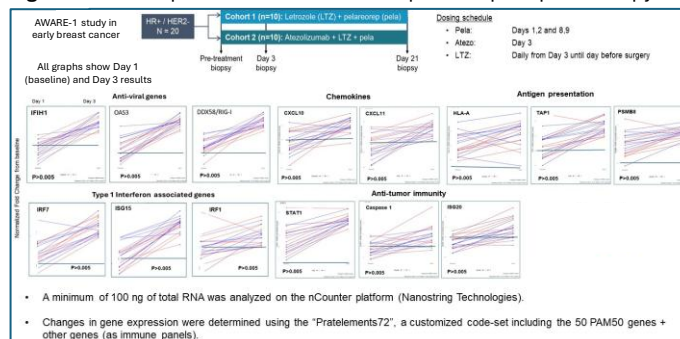


Conclusions

- Pela induces anti-viral responses that broadly upregulate immune genes in tumors
- Pela-induced CXCL13 upregulation contributes to TLS formation, which can support TIL expansion
- In pela-treated PDAC patients, TIL clonal expansion in the blood is associated with tumor responses
- Expanded TILs in PDAC include KRAS-specific clones, which are associated with tumor responses

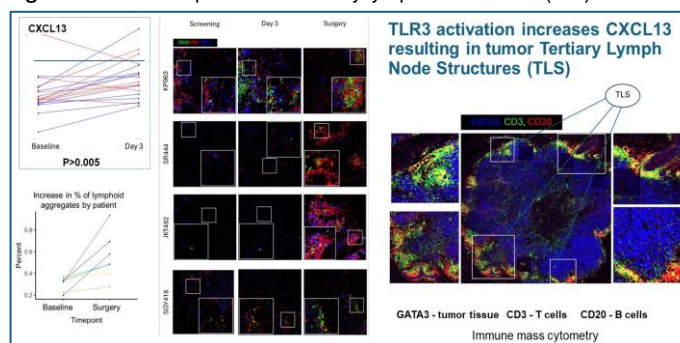
Results

Figure 2. Gene expression in breast tumors pre- and post-pela therapy



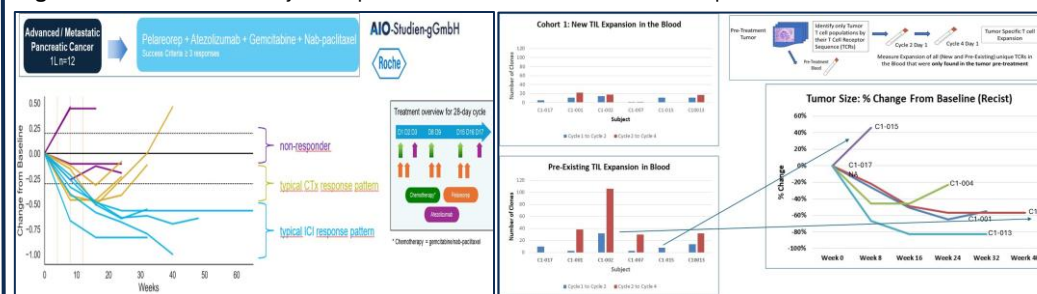
Significant increases in anti-viral and immune gene expression were observed on Day 3 following pela therapy.

Figure 3. CXCL13 expression & tertiary lymphoid structure (TLS) formation



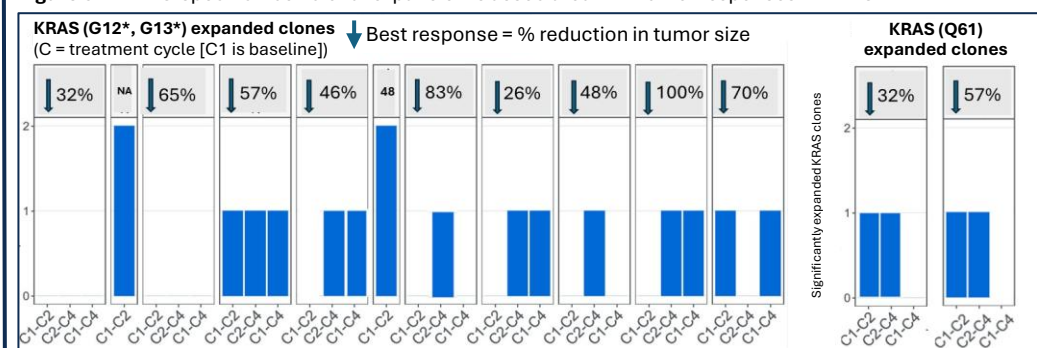
Pela activates TLR3 which induces CXCL13 expression resulting in TLS formation.

Figure 4. GOBLET PDAC study: TIL expansion was associated with tumor responses



Expansion of pre-existing TILs in blood is associated with tumor responses.

Figure 5. mKRAS-specific T cell clonal expansion is associated with tumor responses in PDAC



TCR analysis demonstrated the expansion of mKRAS-specific T cell clones in PDAC patients treated with pela. The development of mKRAS clones was associated with tumor responses.

Acknowledgements

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