T Cell Receptor Sequencing to Monitor Pelareorep-Induced Expansion of Tumor Infiltrating Lymphocytes

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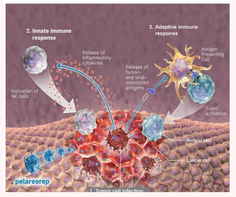
BACKGROUND

Pelareorep (pela) is an intravenously (IV) delivered and systemically available unmodified oncolytic reovirus that can replicate in tumor tissue and induce an inflamed T cell phenotype.



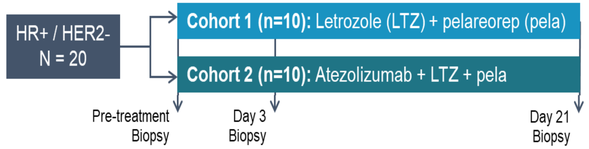
Pelareorep mechanism of action. Pelareorep selectively infects cancer cells leading to tumor cell lysis. The virus also mediates anti-tumor immunity by activating both innate and adaptive immune response.

- **Naturally occurring reovirus isolate**
  - Double-stranded RNA genome
  - Non-pathogenic, not genetically modified
- **Intravenous administration enables systemic activity**
  - Directly targets both primary and metastatic tumors
  - Safe and simple administration in the chemotherapy suite
  - Facilitates delivery of booster doses
- **Selectively replicates in cancer cells and induces an inflamed tumor phenotype**
- **Favorable safety profile demonstrated in over 1,100 treated patients**

Tumor infiltrating lymphocytes (TILs) represent a major immunological tumor control mechanism and is associated with a better prognosis in breast cancer patients. We have previously reported the effect of pela on a composite measurement of TILs and tumor cellularity (CelTIL) from the AWARE-1 study. These results showed a treatment-induced increase in CelTIL scores that was enhanced by atezolizumab. To confirm and extend these findings, we applied T cell receptor sequencing (TCR-seq) of matched tumor tissue and whole blood pre- and post-treatment from AWARE-1 patients to further explore the effects of pela therapy on TILs.

STUDY DESIGN & METHODS

- AWARE-1 is a window-of-opportunity study evaluating the safety and effects of letrozole + pela ± atezolizumab on the tumor microenvironment (TME) in women with early breast cancer.



- Methods: Newly diagnosed HR+/HER2- early breast cancer (eBC) patients were enrolled into two cohorts: Cohort 1: pela + letrozole (n=10); and Cohort 2: pela + letrozole + atezolizumab (n=10). Pela was administered on Days 1, 2 and 8, 9, and atezolizumab was given on Day 3. Tumor biopsies (FFPE samples) collected pre-treatment (~D-23) and on Day 21, when tumors were surgically removed. T cell fraction and T cell receptor sequencing were analyzed by Adaptive Biotechnology's (Seattle, Washington) Immunoseq protocol.

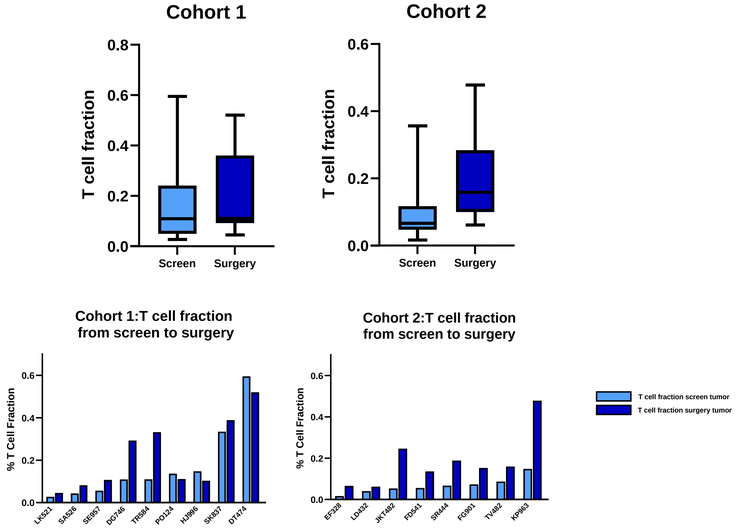
RESULTS

CelTIL score - Cohort 2 achieved the study's primary endpoint

- CelTIL score = −0.8 × tumor cellularity (in %) + 1.3 × TILs (in %).
- An increase in CelTIL score is associated with better treatment outcomes
- Cohort 2 has achieved the study's primary endpoint with 60% of patients showing an increase in CelTIL ≥30% (Manso et. al. 2021 AACR)

Pelareorep induced changes in T cell fraction

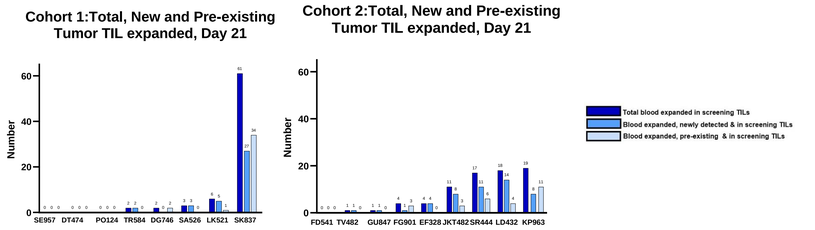
- Tumor infiltrating lymphocytes (TILs) were assessed by T cell fraction in pre- and post-treatment (Day 21) tumor biopsies.
- Median T cell fraction values for each cohort are shown in the top figure
- T cell fraction by subject is shown in the lower figure
- While both groups showed a mean increase in tumor T cell fraction, there was a greater increase in Cohort 2 than in Cohort 1 (1.27 vs 2.74-fold increase)



RESULTS

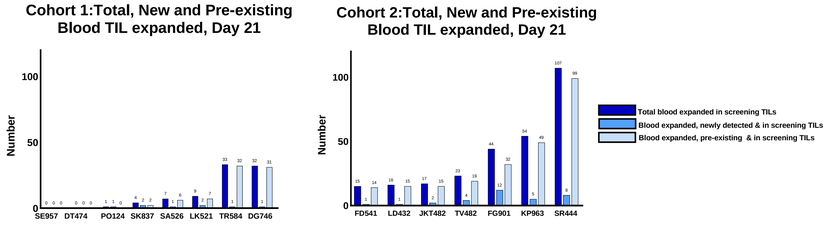
Clonal Expansion of TILs in the tumor

TIL clones were identified by sequencing the T cell receptor. The expansion of TIL-specific clones in the tumor post treatment is shown for Cohort 1 and Cohort 2



Clonal expansion of TILs in the blood

TIL clones were identified by sequencing T cell receptor. The expansion of TIL specific clones in the blood post treatment is shown for Cohort 1 and Cohort 2



CONCLUSION

- These results confirm the previously reported CelTIL results from AWARE-1 demonstrating pela-induced increases in TILs post-treatment
- Clonal expansion of TILs was also observed in the blood
- Newly detected TIL clones were more prominent in the tumor
- Pre-existing TIL clones were more prominent in the blood