Changes in T cell clonality in AWARE-1 study: a window-of-opportunity study with atezolizumab and the oncolytic virus celtil in early breast cancer

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BACKGROUND
- Pelareorep (CEL) is an intravenously (iV) delivered oncolytic reovirus that can replicate in tumor tissue and induce T cell infiltrated phenotype (Figure 1).
- A previous phase 2 study in metastatic breast cancer (BC), known as IND-213, compared treatment with pexi, in combination with paclitaxel (PTX) versus PTX alone. This study demonstrated a statistically significant improvement in overall survival (OS). We hypothesized that the OS from pexi + PTX may be due to an additional immune response triggered by pexi. In this study, we designed a window of opportunity study (AWARE-1) within the “Window Program” of SOLTI, which is currently enrolling, to assess the biological activity of pexi in different BC types in combination with anti-PD-L1 therapy, anti-EGFR, and anti-HER2 treatment (NCT04121816).
- The primary endpoint of the study is CelTIL score, a metric for quantifying the changes in tumor cellularity and tumor infiltrated lymphocytes (TILs), where an increase in CelTIL is associated with a favorable response to treatment.

RESULTS
- To date, 23 patients from 13 different hospitals in Spain have been included in the study. Here, we report initial translational results focusing on cohort 1 (n=10):

- **CeTIL and pelareorep replication in tumor biopsies following IV delivery**
  - **Figure 3.** CeTIL score from cohort 1. CeTIL is calculated with the following equation: CeTIL score = 1.6 x tumor cellularity (in %) + 1.3 x TILs (in %). The maximum and minimum CeTIL scores will be set to 40 and 13, respectively. The unscaled CeTIL score is then reflected to a range of 0 to 100 points.
  - **Figure 4.** Pelareorep replication assessed by immunohistochemistry.
    - **Productive reoviral infection is seen in all post-treatment tumor biopsies, averaging 52% of tumor cells at day 3 and 43% at day 7.**
    - **Viral replication was not observed in adjacent normal tissue.**
    - **Viral deRNA (an immune adjuvant) is observed in a higher proportion of tumor cells than viral protein (not shown).**
    - **Treatment with pelareorep promotes the creation of new T cell clones**

- **Figure 5.** Changes in CeTIL T cell infiltration
  - **All patients had an increase in CeTIL T cells at surgery (day 21).**
  - **There was a 14-fold increase in intratumoral CeTIL T cells from baseline to surgery (ranging from 0.4 to 41).**
  - **There is a high degree of tumor burden and immune response at tumor cellularity will be correlated with tumor burden and immune response**
  - **Viral deRNA (an immune adjuvant) is observed in a higher proportion of tumor cells than viral protein (not shown).**

- **Figure 6.** Clonal expansion in peripheral blood and tumor
  - **Increased T cell counts and clonality are seen in the peripheral blood.**
  - **Aromatic amino acid decarboxylase (AADC) was present at baseline, which suggests an immune response to pelareorep.**
  - **This motif was also expanded in patients from previous studies with pelareorep.**

- **Figure 7.** New T cell clones are expanded in the tumor and peripheral blood
  - **Many of the expanded clones in the tissue are also expanded in the peripheral blood.**
  - **The majority of expanded clones represent new clones from the peripheral adoptive T cell therapy (pTCR-TCR) and a minimal response in clonal expansion in pts SK837, LK521, and HJJ995 suggests the expansion of tumor-antigen-specific CD8+ T cells**

- **RESULTS**

- **Common clones were expanded in multiple patients**

STUDY DESIGN

STUDY OBJECTIVES

Primary objective: to evaluate CelTIL score increasing follow 3 weeks of treatment in each cohort.

Secondary objective: to evaluate immunological changes within the tumor and peripheral blood.

CONCLUSION

- Following a previous mBC study with pelareorep, we hypothesized that the survival advantage of patients treated with pelareorep + pexi was due to pelareorep’s ability to create an anti-CD19+ T cell therapy in breast cancer patients that exceeded the therapeutic efficacy of the pexi alone. Preliminary data from cohort 1 of AWARE-1 supports this hypothesis.

- We have reached the dose and schedule of pelareorep + pexi with efficacy and tolerability as expected. These results are consistent with the findings in other studies published in clinical trials.

- **Within the expanded pool of new T cell clones following pelareorep therapy, we identified both presumptive anti-tumor and anti-viral T cell clones.**

- **Given the absence of checkpoint blockade therapy in cohort 1, a 70% CeTIL response rate is encouraging. Interestingly, the degree of viral replication (protein) does not correlate with changes in CeTIL. One explanation for this observation is that viral RNA, rather than viral protein, may be a better correlate marker since only viral RNA binds to a known immune adjuvant that can trigger inflammatory signaling pathways.** This research, along with additional correlations, suggests that the future of these treatments is promising.

- **Results from IND-2TP1, AWARE-1, & ABRACELT-1 studies will be used to inform a future registration study in mBC.**

REFERENCES