Changes in T Cell Clonality in AWARE-1 Study, a Window-of-Opportunity Study with Atezolizumab and the Oncolytic Virus Pelareorep in Early Breast Cancer

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Background A previous phase 2 study in metastatic breast cancer demonstrated a statistically significant improvement in overall survival (OS) in patients treated with pelareorep (pela) in combination with paclitaxel (PTX) versus PTX alone. Given that pela is an intravenously delivered immuno-oncolytic reovirus, we hypothesized that the OS benefit from pela + PTX may be attributed to an adaptive T cell response triggered by pela. To examine if pela can mediate the priming of an anti-tumor immune response, we are conducting together with the SOLTI group the AWARE-1 study (a window-of-opportunity study of pela in early breast cancer), which is currently enrolling and for which initial translational research results are presented.

Methods AWARE-1 is a window-of-opportunity study to evaluate the safety and effect of pela ± ateziolubam on the tumor microenvironment (TME) in 38 women with early breast cancer. Patients are treated with pela on days 1, 2, 8, and 9, while atezolizumab is administered on day 3. Tumor biopsies are collected at diagnosis, day 3, and day −21. Five cohorts will be examined: Cohort 1: HR+/HER2-neg (10 patients) receiving pelareorep + letrozole; Cohort 2: HR+/HER2-neg (10 patients) receiving pelareorep + letrozole + ateziolubam; Cohort 3: TNBC (6 patients) receiving pelareorep + ateziolubam; Cohort 4: HER2+/HR+ (6 patients) receiving pelareorep + trastuzumab + ateziolubam; Cohort 5: HER2+/HR+ (6 patients) receiving pelareorep + trastuzumab + ateziolubam. The primary endpoint of the study is CeiTIL score, a metric for quantifying the changes in tumor cellularity and infiltration of TILs, where an increase in CeiTIL is associated with a favorable response to treatment. Tumor tissue is being examined for pela replication, and changes to the TME are being assessed by immunohistochemistry and T cell receptor sequencing (TCR-seq). Peripheral blood is also being examined by TCR-seq.

Results Detailed TCR-seq results from peripheral blood and tumor tissue are presented for the ten-patients enrolled into Cohort 1 who received pela and letrozole. In tumor tissue, T cell clonality increased in day 21 biopsies relative to baseline biopsies, with similar increases in T cell fraction (the number of T cells) in the majority of patients. In general, most of the tissue-expanded T cell clones were also seen in the peripheral blood.

Conclusions Overall, these preliminary data from cohort 1 of AWARE-1 demonstrate that pela mediates priming of a T cell-based immune response that occurs both systemically and within breast cancer tissue.

Trial Registration NCT04102618

Ethics Approval This study was approved by the Spanish Health Authority, protocol number 2018-003345-42.