BACKGROUND

Parellorep (pela) is an intravenously delivered (IV) unmodified oncolytic reovirus that can replicate in tumor tissue and induce a T-cell-inflamed phenotype1 (Figure 1).

A previous phase 2 study in metastatic breast cancer (BC) compared treatment with pela, in combination with paclitaxel (PTX) versus PTX alone. This study demonstrated a statistically significant improvement in overall survival (OS). We hypothesized that the OS benefit from pela + PTX may be attributed to an adaptive immune response triggered by pela.

To test this hypothesis, we designed a window of opportunity study (AWARE-1) within the “Window Program” at the National Cancer Institute to evaluate the biological activity of pela in different BC types in combination with anti-PD-L1 therapy, atezolizumab, and other BC therapies (NCT04020181).

The primary endpoint of the study is CeTIL score2, a metric for quantifying the changes in tumor cellularity (Cel) and tumor infiltrated lymphocytes (TILs), an increase in CeTIL is associated with a favorable response to treatment.

STUDY OBJECTIVES

Figure 1. Parellorep mechanism of action. Parellorep selectively infects cancer cells leading to tumor cell lysis. The virus also mediates anti-tumor immunity by activating both innate and adaptive immune response. We hypothesized that pela mediated inflammation will boost anti-PD-L1 response.

- PRIMARY OBJECTIVE: to evaluate CeTIL score increase at 3 weeks of treatment of each cohort.
- KEY SECONDARY AND EXPLORATORY OBJECTIVES:
  - To describe safety and tolerability of the different therapies and combinations.
  - To evaluate biological changes to response to study drug(s), including 60 breast cancer-related genes and a panel of 770 immune-related genes.
  - To examine CD8+ and CD8+ T-cell expansion and baseline and treated samples. DNA seq of T-cell receptor repertoire.
  - To evaluate whether pelareorep with different therapies induce different immune blood markers, such as changes in peripheral blood mononuclear cell.

RESULTS

- Up to day 13. 13 patients from 6 different hospitals in Spain have been included in the study. Here, we report initial translational results of the first 6 patients.

Pelareo replication and immunological changes within the tumor microenvironment (TME)

- Analysis of CeTIL show an increase in four of the six patients.
- Productive viral replication in day 3 and day 21 biopsies (surgery) was very high.
- Immunohistochemistry analysis revealed an increase in CD68+ T-cells and upregulation of PD-L1 on day 3 and day 21 biopsies for all patients.

Table 1. Percentage of virus positive cells, percentage of change in CeTIL score and fold change in PD-L1 + cells and CD8+ cells (surgery vs screening).

- The degree of viral replication was consistent with changes in CeTIL and within immunological changes in the TME, mainly CD8+ T-cell infiltration and PD-L1 expression. 
- Preliminary data from the first six patients in AWARE-1 demonstrate pela-mediated priming of an adaptive immune response, helping to validate our hypothesis that the extended OS observed in our prior study1 can be attributed to pela-mediated T-cell priming.
- Following initial treatment (~3 weeks), peripheral T-cell clonality may be correlated with changes in CeTIL and clinical response as seen in prior studies1.