A window-of-opportunity Study with atezolizumab and the oncolytic virus pelareorep in early Breast Cancer (REO-027, AWARE-1)

Luis Manso[1], Patricia Villagrasa[2], Nuria Chic[3], Begoña Bermejo[4], Juan Miguel Cejalvo[4], Yann Izarzugaza[5], Blanca Cantos[6], Salvador Blanch[7], Mireia Margeli[8], Jose Luis Alonso[9], Alejandro Martínez[10], Rafael Villanueva[11], Juan Antonio Guerra[12], Raquel Andrés[13], Pilar Zamora[14], Esteban Nogales[15], Manel Juan[3], Blanca Gonzalez-Farre[16], Thomas C. Heineman[17], Gerard Nuovo[18], Grey Wilkinson[17], Matt Coffey[17], Azucena Gonzalez[3], Débora Martínez[3,20], Laia Paré[2], Fernando Salvador[2], Xavier Gonzalez[19], Aleix Prat[2,3,20,21], Joaquín Gavilá[7].

[1]Hospital Universitario 12 de Octubre, Madrid, Spain. [2]SOLTI Breast Cancer Research Group, Barcelona, Spain. [3]Medical Oncology Department, Hospital Clínic de Barcelona, Barcelona, Spain.[4]Hospital Clínico Universitario de Valencia, INCLIVA (Instituto de investigación sanitaria) and CIBERONC, Valencia, Spain [5]Hospital Universitario Fundación Jiménez Díaz, Madrid, Spain. [6]Hospital Universitario Puerta de Hierro-Majadahonda, Madrid, Spain. [7]Instituto Valenciano de Oncología (IVO), Valencia, Spain. [8]Medical Oncology Department, ICO Badalona, Institut Català d'Oncologia, Barcelona, B-ARGO Group, Spain. [9]Hospital Clínico Universitario Virgen de la Arrixaca-IMIB., Murcia, Spain. [10]Medical Oncology Department, Hospital Universitari Quirón Dexeus, Barcelona, Spain [11]Hospital Moisès Broggi, Sant Joan Despí, Barcelona, Spain. [12]Hospital Universitario de Fuenlabrada, Madrid, Spain. [13]Hospital Clínico Universitario Lozano Blesa, Zaragoza, Spain. [14]Medical Oncology Department, Hospital Universitario La Paz, Madrid, Spain. [15]Hospital Universitario Virgen Macarena, Sevilla, Spain. [16]Pathology department Hospital Clinic de Barcelona, Barcelona, Spain. [17]Oncolytics Biotech Inc. [18]Ohio State University Arthur G. James Cancer Hospital and Richard J. Solove Research Institute, Columbus, OH. [19]Hospital Universitari General de Catalunya, Sant Cugat del Vallés, Spain. [20]August Pi i Sunyer Biomedical Research Institute (IDIBAPS), Barcelona, Spain. [21]Medicine Department, University of Barcelona, Barcelona, Spain

San Antonio Breast Cancer Symposium® - December 8-11, 2020. PS12-08

BACKGROUND

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

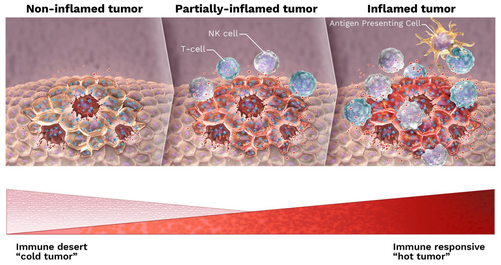


Figure 1. Pelareorep mechanism of action. Pelareorep selectively infects cancer cells leading to tumor cell lysis. The virus also mediates anti-tumor immunity by activating both innate and adaptive immune response. We hypothesize that pelareorep mediated immune responses will boost anti-PD-L1 response.

- A previous phase 2 study in metastatic breast cancer (BC), known as IND.213, compared treatment with pela, in combination with paclitaxel (PTX) versus PTX alone[2]. 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" of SOLTI to assess the biological activity of pela in combination with the anti-PD-L1 therapy, atezolizumab, and other BC therapies in different BC types with an emphasis on HR-pos/HER2-neg BC (NCT04102618)
- The **primary endpoint of the study is CelTIL score[3]**, 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.

STUDY DESIGN

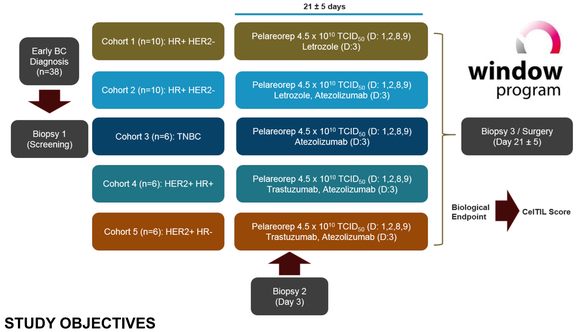


Figure 2. Study design. Patients are treated with pela on days 1, 2, 8, and 9, while atezolizumab is administered on day 3 (excluding cohort 1). Tumor biopsies are collected at diagnosis, day 3, and day ~21.

STUDY OBJECTIVES

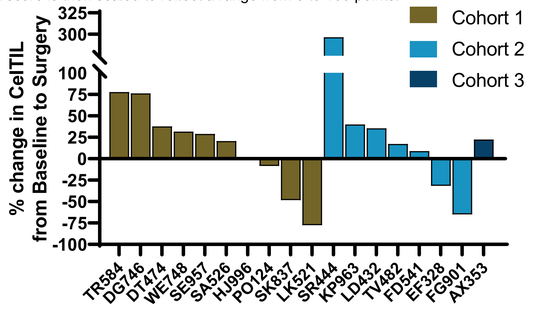
- Primary objective: to evaluate CelTIL score increase following 3 weeks of treatment in each cohort.
- Secondary objective: to evaluate immunological changes within the tumor and peripheral blood.

RESULTS

- To date, 23 patients from 13 different hospitals in Spain have been included in the study.

CelTIL score

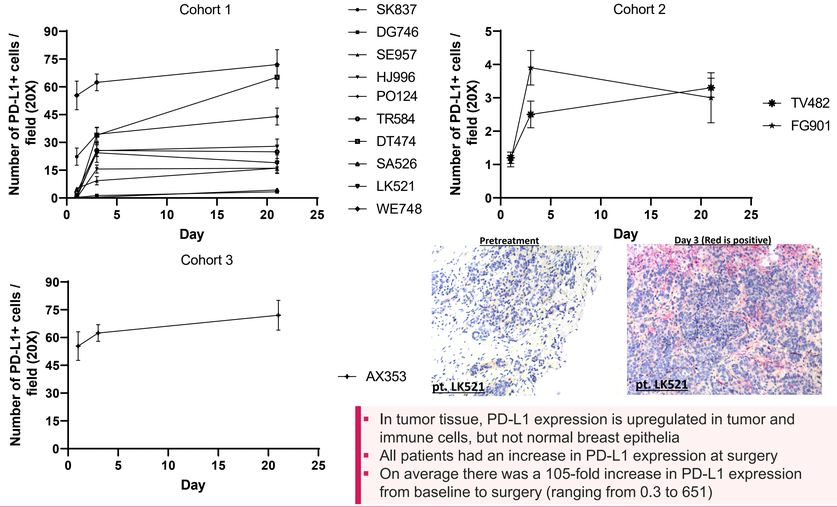
Figure 3. CelTIL score from the first 18 patients. CelTIL is calculated with the following equation: CelTIL score = −0.8 × tumor cellularity (in %) + 1.3 × TILs (in %). The minimum and maximum unscaled CelTIL scores will be −80 and 130. This unscaled CelTIL score is then scaled to reflect a range from 0 to 100 points.



- An increase in CelTIL is associated with better treatment outcomes.
- There is a 72% CelTIL response rate irrespective of cohort.

Treatment with pelareorep promotes PD-L1 expression in the tumor microenvironment (TME)

Figure 4. Changes in PD-L1 expression from the first 13 patients assessed by immunohistochemistry.

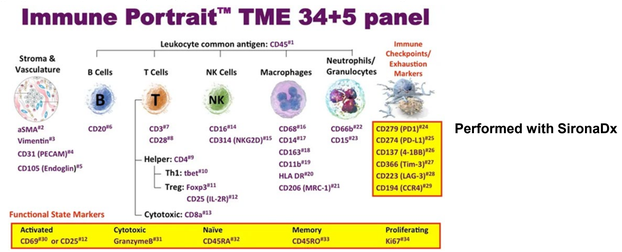


- In tumor tissue, PD-L1 expression is upregulated in tumor and immune cells, but not normal breast epithelia
- All patients had an increase in PD-L1 expression at surgery
- On average there was a 105-fold increase in PD-L1 expression from baseline to surgery (ranging from 0.3 to 651)

RESULTS

Pelareorep mediated changes in the TME characterized by imaging mass cytometry

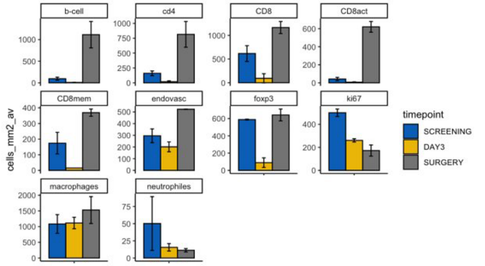
Figure 5. Imaging mass cytometry (IMC) panel used to characterize changes in the TME



Performed with SironaDx

Preliminary IMC analysis demonstrates that treatment with pelareorep promotes broad changes in the TME

Figure 6. Preliminary IMC analysis for patient SE957



- In patient SE957, treatment with pelareorep promotes the recruitment of B cells and CD4 and CD8 positive T cells to the TME.
- Treatment also promotes T cell activation (CD8+;CD69) and recruitment of memory T cells (CD8+;CD45RO+).

CONCLUSION

- To date, the study has achieved an encouraging 72% CelTIL response rate from 18 patients.
- Following a previous metastatic BC study with pelareorep, we hypothesized that the survival advantage of patients treated with pelareorep + PTX was due to pelareorep's ability to create an anti-viral or anti-tumor T cell response in breast cancer that promotes therapeutic efficacy. Preliminary data from AWARE-1 supports this hypothesis.
- While IMC analysis is ongoing, preliminary results from patient SE957 demonstrate that treatment with pelareorep can prime the tumor microenvironment for checkpoint blockade therapy and promote a T cell based response in breast cancer tissue.
- Results from this and other BC studies (IND.213[2] & BRACELET-1[4]) will inform a future registration study in metastatic BC.

References

[1] Samson et al. Sci Transl Med 2018;10. [2] Bernstein et al. Breast Cancer Res Treat 2018;167:485-93. [3] Nuciforo et al. Ann Oncol (2018), 29: 170-77. [4] clinicaltrials.gov: NCT04215146.