A window-of-opportunity Study of pelareorep in Early Breast Cancer (AWARE-1)

Luis Manso[1], Patricia Villagrasa[2], Nuria Chic[3], Juan Miguel Cejalvo[4], Yann Izarzugaza[5], Blanca Cantos[6], Salvador Blanch[7], Manel Juan[3], Blanca Gonzalez[3], Rita Laeufle[8], Gerard Nuovo[9], Grey Wilkinson[8], Matt Coffey[8], Azucena Gonzalez[3], Patricia Galvan[3], Laia Paré[2], Jordi Canes[2], Fernando Salvador[2], Xavier Gonzalez[10], Aleix Prat[2,3]Joaquín Gavilá[7].

1 Hospital Universitario 12 de Octubre, Madrid; 2 SOLTI Breast Cancer Research Group, Barcelona; 3 Hospital Clinic, Barcelona; 4 Hospital Clínico Universitario de Valencia ; 5 Hospital Universitario Fundación Jiménez Díaz ; 6 Hospital Universitario Puerta de Hierro-Majadahonda ; 7 Instituto Valenciano de Oncología (IVO) ; 8 Oncolytics Biotech Inc.; 9 Ohio State University Arthur G. James Cancer Hospital and Richard J. Solove Research Institute, Columbus, OH. ; 10 Hospital Universitari General de Catalunya, Sant Cugat del Vallés, Spain.

BACKGROUND

- Pelareorep is an intravenously delivered (IV) unmodified oncolytic reovirus. Clinical studies have demonstrated that IV delivered pelareorep can replicate in tumor tissue and promote an inflamed tumor phenotype characterized by the recruitment of CD8+ T cells and upregulation of PD-L1[1] (Figure 1).

- Consistent with pelareorep's role in promoting adaptive anti-tumor immunity, a randomized phase 2 study in metastatic breast cancer (BC) patients, who had received at least one prior palliative chemotherapy regimen, demonstrated a statistically significant improvement in overall survival when pelareorep was combined with paclitaxel[2].

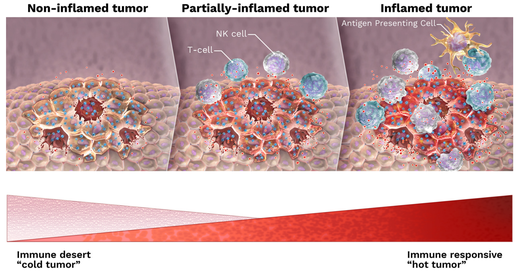
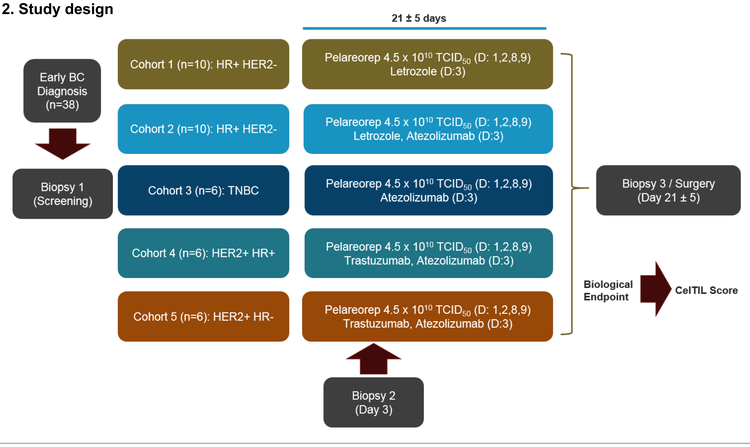


Figure 1. Pelareorep mechanism of action. Pelareorep selectively infects cancer cells leading to tumor cell lysis. The virus also mediates anti-tumor immunity by activating both innate and adaptive immune response. We hypothesize that pelareorep mediated inflammation will boost anti-PD-L1 response.

- AWARE-1 is a window opportunity study within the **"Window Program" of SOLTI** designed to assess the biological activity of pelareorep in different BC types in combination with anti-PD-L1 therapy, atezolizumab, and other BC therapies. Primary objective is to evaluate changes in CelTIL score, a metric for quantifying tumor cellularity (Cel) and tumor-infiltrating lymphocytes (TIL). Importantly, an increase in CelTIL score has been correlated with positive patient outcome in several scenarios including anti-HER2 based therapy[3]. Positive signals from this study would provide strong evidence for further clinical investigations aimed to increase the pCR rate at early setting.
- This study was approved by the Spanish Health Authority, protocol number 2018-003345-42 (NCT04102618).

STUDY DESIGN

Figure 2. Study design



INITIAL SAFETY PHASE: the first 3 subjects enrolled in cohorts that include pelareorep and atezolizumab (2 to 5) will undergo close monitoring to evaluate safety of the combination. Once completed the treatment period of 3 patients, the recruitment will be stopped until evaluation by the Steering Committee.

- **PRIMARY OBJECTIVE:** to **evaluate CelTIL score** increase at 3 weeks of treatment of each cohort.
- **KEY SECONDARY AND EXPLORATORY OBJECTIVES:**
  - To describe **safety and tolerability** of the different drug combinations.
  - To evaluate **biological changes to predict response** to study drug(s), including 60 breast cancer-related genes and a panel of 770 immune-related genes.
  - To examine **CD4 and CD8-T cell reactivity** between baseline and treated samples
  - To evaluate whether pelareorep with different therapies induce **different immune blood markers,** such as changes in peripheral blood mononuclear cells.

CURRENT STATUS

Preliminary results from tissue biopsies

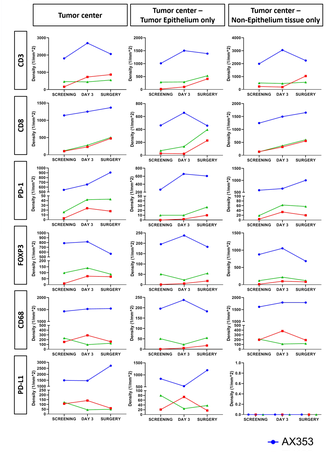
Table 1: Reoviral replication

Patient	Time-point	Reoviral RNA (% of tumor cells+)	Reoviral protein (% of tumor cells+)
AX353 (Cohort 3)	Screening	0	0
	Day 3	69.4 (13.1)	61.4 (9.1)
	Surgery	72.3 (9.8)	64.9 (8.4)
TV482 (Cohort 2)	Screening	0	0
	Day 3	57.9 (11.1)	52.3 (9.1)
	Surgery	60.3 (9.9)	51.9 (8.9)
FG901 (Cohort 2)	Screening	0	0
	Day 3	4.3 (1.1)	3.0 (0.9)
	Surgery	3.2 (0.9)	2.1 (0.8)

Table 2: Changes in CelTIL

Patient	Time-point	Tumor Cellularity	TILs	CelTIL
AX353 (Cohort 3)	Screening	60	20	27.6
	Day 3	50	20	31.4
	Surgery	60	30	33.8
TV482 (Cohort 2)	Screening	50	5	22.0
	Day 3	40	5	26.0
	Surgery	40	5	26.0
FG901 (Cohort 2)	Screening	40	1	23.5
	Day 3	50	1	19.7
	Surgery	80	1	8.2

Figure 3: Changes in the immune cells



PATIENT STATUS: up to date **6 patients have been included** in the study. After the safety phase (3 subjects), recruitment re-started (Figure 4 and Table 3). There are currently 6 activated sites.

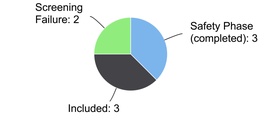


Figure 4. Patient status.

	Cohort-1	Cohort-2	Cohort-3	Cohort-4	Cohort-5
Safety Phase	x	2	1	x	x
Post-Safety Phase	3	x	x	x	x
Screening Failure	2	x	x	x	x

Table 3: Patient status.

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3. Nuciforo, P., Pascual, T., Cortés, J., Llombart-Cussac, A., Fasani, R., Paré, L., ... Holgado, E. (2018). A predictive model of pathologic response based on tumor cellularity and tumor-infiltrating lymphocytes (CelTIL) in HER2-positive breast cancer treated with chemo-free dual HER2 blockade. Annals of Oncology. https://doi.org/10.1093/annonc/mdx647