# Role of pelareorep in activating anti-tumor immunity in PDAC

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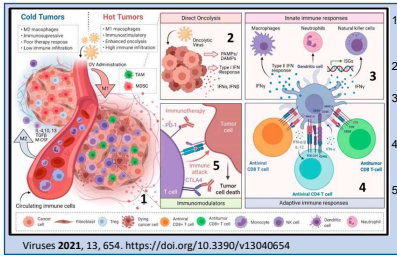
## Background

Pancreatic ductal adenocarcinoma (PDAC) is highly lethal cancer with limited therapeutic options. Pelareorep (pela) is an intravenously delivered unmodified reovirus containing a double stranded RNA genome that has been studied as an immunotherapeutic in pancreatic, breast, anal, colorectal and other cancers. We previously reported high tumor response rates in first-line metastatic PDAC patients treated with pela combined with gemcitabine, nab-paclitaxel and atezolizumab. We report here the immunologic effects of pela in a cohort of first-line metastatic PDAC patients treated with pela plus chemotherapy and atezolizumab and the correlation of these effects with tumor response.

**Pela promotes a pro-inflammatory tumor microenvironment (TME) and induces innate and adaptive immune responses**




1) Pela infection delivers dsRNA, a powerful immune stimulant, to the tumor which induces an inflamed TME
2) Pela infection kill tumor cells causing the release of tumor antigens
3) Immune stimulatory molecules are released to activate and enhance anti-viral and anti-tumor immune responses
4) Both anti-viral and anti-tumor cytotoxic T cells are expanded and can enter the tumor and target tumor cells
5) Cytotoxic T cell activity can be enhanced by other immune enhancing therapies, such as checkpoint inhibitors, to maximize anti-tumor responses

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**Methods**:

Design: Phase 1/2, Simon two-stage platform study

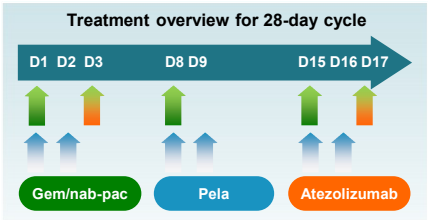
Population: 1st-line locally advanced/metastatic unresectable PDAC

Primary endpoints: Safety and tumor response per RECIST v.1.1

Immunologic assessments:

- Anti-reovirus T cell activity by interferon-γ secretion (ELISPOT)
- Plasma protein levels by Olink proteomics immune panel profiling
- T cell receptor sequencing (TCR-seq; Adaptive Biotechnologies) to identify tumor-infiltrating lymphocyte (TIL) clonal expansion. Samples tested included baseline tumor and blood (collected prior to therapy) and blood collected through 3 treatment cycles.

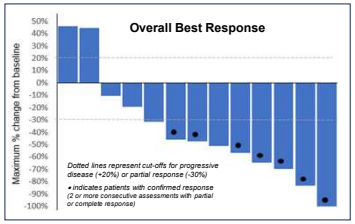
## GOBLET Study Overview (Eudra-CT #:2020-003996-16)

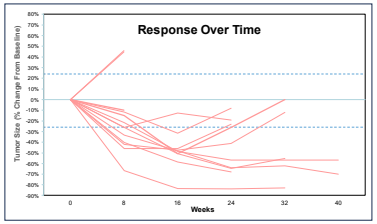



**Results Summary**

- All evaluable patients had metastatic disease
- Average age: 62 years (range: 49-76)
- 85% male
- 69% had liver metastases
- Treatment well-tolerated with no unexpected safety concerns

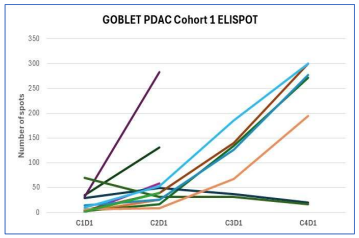
## Clinical Response



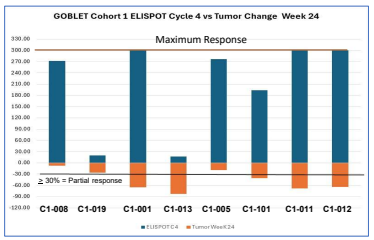




| ORR | DCR | 12-month survival rate |
|---|---|---|
| 62% (54% confirmed) | 85% | 45% |

## Translational Evaluations: Anti-reovirus Response



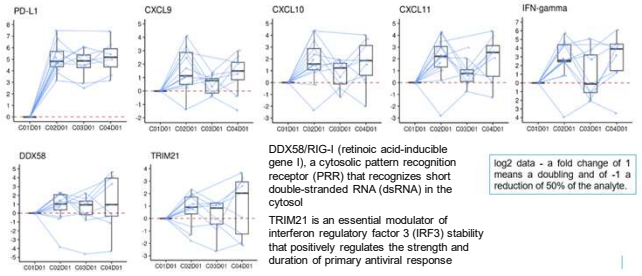

ELISPOT Response over time
C1D1 – Cycle 1 Day 1




ELISPOT Response, Tumor volume and Clinical Response at Week 24

## Olink Response Panel Data

**Therapy increases expression of chemokines, cytokines and anti-viral proteins in plasma**

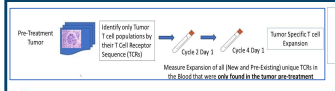



DDX58/RIG-I (retinoic acid-inducible gene I), a cytosolic pattern recognition receptor (PRR) that recognizes short double-stranded RNA (dsRNA) in the cytosol

TRIM21 is an essential modulator of interferon regulatory factor 3 (IRF3) stability that positively regulates the strength and duration of primary antiviral response

log2 data - a fold change of 1 means a doubling and of -1 a reduction of 50% of the analyte.

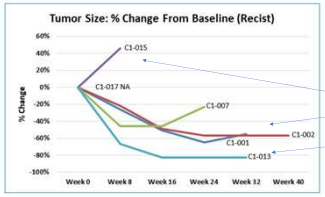
## TIL Clonal Expansion Associated with Tumor Response

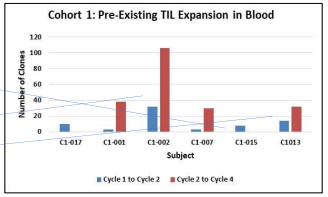




Bsl – Baseline; C1D1 - Cycle 1 Day 1

Jaccard Index: Shared TIL clones in blood and tumor




## Conclusions

- Pela activates interferon-γ secreting anti-virus T cells
- Olink response data show increases in plasma markers associated with a hot tumor phenotype
- Tumor responses correlate with TIL clones in the blood prior to treatment and the expansion of pre-existing TILs in the blood on treatment
- These findings support pela as a novel immunotherapeutic that may provide clinical benefit in patients with metastatic PDAC