Preliminary Safety and Tumor Response Results for the Relapsed Anal Carcinoma Cohort in Patients Treated with Pelareorep and Atezolizumab

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Background

This study evaluates safety and efficacy of pelareorep + atezolizumab as 2nd-line therapy in relapsed unresectable squamous cell carcinoma of the anal canal (SCCA).

SCCA patients with relapsed disease have limited treatment options. Checkpoint inhibitor monotherapy is recommended, but response rates are low (10-24%). Immune-based therapies that induce an inflammatory tumor microenvironment (TME) may improve the susceptibility of SCCA to checkpoint inhibitors. Pelareorep (pela) is a non-genetically modified, IV administered reovirus that stimulates the expansion of tumor-infiltrating lymphocyte (TIL) clones and makes tumors visible to the immune system by upregulating interferon-induced gene expression including PD-L1, CXCL9, CXCL10, and CXCL11. Pelareorep combined with chemotherapy, checkpoint inhibitors, or both has shown promising efficacy in several malignancies, including metastatic pancreatic cancer and HR-positive/HER2-negative breast cancer.

Pela-based combination therapy offers a promising new treatment approach for patients with SCCA.

Pelareorep Mechanism of Action

Pela induces anticancer adaptive immune responses and an inflammatory TME:

- Stimulates expansion of TIL clonal populations
- Pela's double-stranded RNA induces expression of interferon-regulated genes, e.g., CXCL9, CXCL10, CXCL11 and PD-L1
- Consequently, pela-treated tumors are visible to the immune system as evidenced by increased T cell infiltration into tumors
- Upregulation of PD-L1 also provides a basis for synergy with checkpoint inhibitors

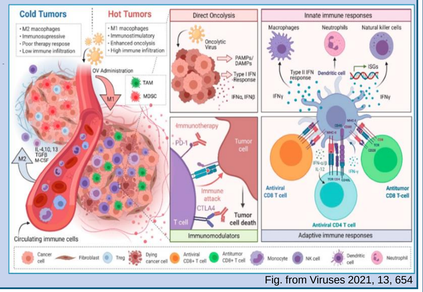


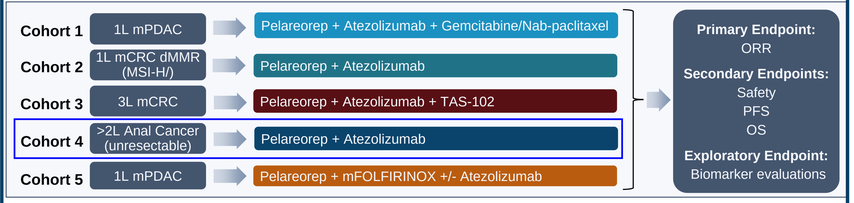
Fig. from Viruses 2021, 13, 654

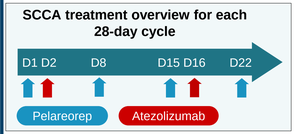
Study Design

- GOBLET is a phase 1/2, open-label, non-randomized, Simon two-stage platform study in patients with advanced or metastatic GI cancers.
- GOBLET Cohort 4 is enrolling patients with locally advanced/metastatic SCCA who failed one or more lines of prior systemic chemotherapy.
- SCCA patients are treated with pela plus atezolizumab (atezo).
- Stage 1 enrolls 10 patients with success defined as ≥2 responses; Stage 2 enrolls 18 evaluable patients with success defined as ≥7 responses out of all 28 evaluable patients.

Study Design (continued)

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





Dosing:
Pela: 4.5 X 10^{10} $TCID_{50}$/dose IV
Atezo: 840 mg/dose IV

Key Enrollment Criteria:

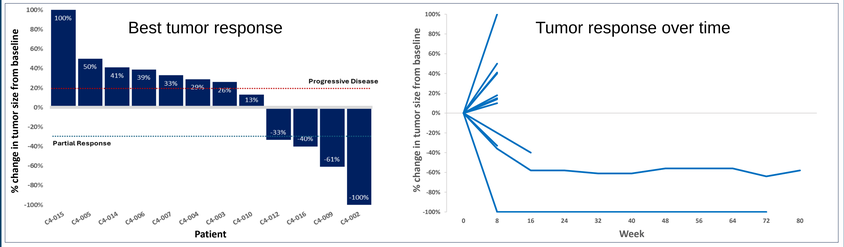
1. 18 years or older
2. Confirmed advanced/metastatic unresectable SCCA
3. Failed and/or did not tolerate prior systemic chemotherapy
4. ECOG performance status of 0 or 1
5. Have a measurable lesion per RECIST v1.1
6. No previous treatment with immune checkpoint inhibitor

Results

Patient characteristics:

Ave. age in yrs	**62 (48-73)**	**ECOG**		**Prior lines of chemotherapy**	
≥65	7 (58%)	0	6 (50%)	1	2 (17%)
<65	5 (42%)	1	6 (50%)	2	2 (17%)
Sex		**Prior radiation therapy**		≥3	8 (67%)
Male	2 (17%)	Yes	9 (75%)	**Baseline PD-L1 expression**	
Female	10 (83%)	No	3 (25%)	Positive	5 (42%)
				Unknown	7 (58%)

Tumor responses (evaluable patients):



Objective response rate = 33%; One prolonged complete response

Results (continued)

Safety

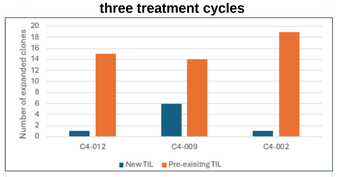
Grade 3 or higher treatment emergent adverse events (TEAEs) in all patients

MedDRA Preferred Term	≥ Grade 3 TEAEs (all patients) Grade 3 N=18 (%)	Grade 4 N=18 (%)	Grade 5 N=18 (%)	All ≥ Grade 3 N=18 (%)
Disease progression	1 (5.6%)	0 (0.0%)	2 (11.1%)	3 (16.7%)
Anemia	2 (11.1%)	0 (0.0%)	0 (0.0%)	2 (11.1%)
AST increased	2 (11.1%)	0 (0.0%)	0 (0.0%)	2 (11.1%)
Cholestasis	2 (11.1%)	0 (0.0%)	0 (0.0%)	2 (11.1%)
Pyrexia	1 (5.6%)	0 (0.0%)	0 (0.0%)	1 (5.6%)
Neutropenia	1 (5.6%)	0 (0.0%)	0 (0.0%)	1 (5.6%)
Musculoskeletal pain	1 (5.6%)	0 (0.0%)	0 (0.0%)	1 (5.6%)
Pulmonary Embolism	1 (5.6%)	0 (0.0%)	0 (0.0%)	1 (5.6%)
ALT increased	1 (5.6%)	0 (0.0%)	0 (0.0%)	1 (5.6%)
Musculoskeletal pain	1 (5.6%)	0 (0.0%)	0 (0.0%)	1 (5.6%)
Alk.phos. increased	1 (5.6%)	0 (0.0%)	0 (0.0%)	1 (5.6%)
Bilirubin increased	1 (5.6%)	0 (0.0%)	0 (0.0%)	1 (5.6%)
Bacteremia	1 (5.6%)	0 (0.0%)	0 (0.0%)	1 (5.6%)
γ-GGT increased	1 (5.6%)	0 (0.0%)	0 (0.0%)	1 (5.6%)

- All patients experienced ≥1 AE; most common (≥Grade 3) were pyrexia, fatigue, chills, nausea, vomiting
- 10/18 patients experienced a ≥ Grade 3 AE (see table)
- Two patients experienced a Grade 5 (fatal) AE, both disease progression

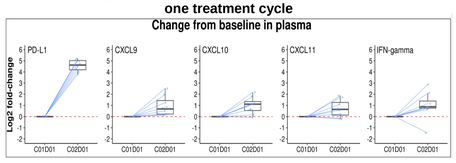
Translational

Expanded new and pre-existing TIL clones through three treatment cycles



TIL clonal expansion in blood. New (not present at baseline) and pre-existing (present at baseline) TIL clones were tracked in blood through treatment Cycle 3.

Upregulated gene products (selected chemokines, etc.) through one treatment cycle



Chemokine upregulation. Plasma levels of PD-L1, CXCL9, CXCL10, CXCL11 and Interferon-γ were determined by Olink assay (Olink Proteomics, Uppsala, Sweden) after 1 cycle of treatment.

- Pela + atezo led to the expansion of new and pre-existing TIL clones in responding patients for which data are available
- Pela + atezo led to the upregulation of multiple chemokines including CLCL9, 10 and 11, as well as PD-L1 and IFN-γ

Conclusions

- No safety signal was observed in relapsed SCCA patients treated with pela + atezo.
- Stage 1 success criteria were met, and Stage 2 enrollment has been initiated.
- Preliminary tumor response rates to pela + atezo are encouraging compared to checkpoint inhibitors alone.
- Expansion of TIL clones in the blood of responding patients is consistent with the known mechanism of action for pela-based therapies.
- Upregulation of PD-L1 expression provides a basis for synergy of pela and CPIs

Pela + atezo shows promise as a treatment for relapsed SCCA