A study of pelareorep in combination with pembrolizumab and chemotherapy in patients (pts) with relapsed metastatic adenocarcinoma of the pancreas (MAP).

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Abstract

Background: Pelareorep (REOLYSIN®) is a immuno-oncolytic virus (IOV) that induces an infected tumor phenotype secondary to viral infection of cancer cells. In combination with chemotherapy, it achieves a 2 to 4 year-survival rates of 46% & 24% in MAP pts, respectively. Tumor analysis from patients (pts) revealed reovirus protein replication, T cell infiltration and upregulation of PD-1/L1. Similarly, the combination of pelareorep with anti-PO-1 antibody documented survival benefit in a pre-clinical model. We hypothesized that pelareorep in combination with chemotherapy and pembrolizumab in pts with MAP would be clinically efficacious.

Methods: A phase 1b study enrolled MAP pts who progressed after first line treatment. Pts received pelareorep (4.5 x 10^9 TCID50, IV, D1 & D2), plus pembrolizumab (2mg/kg IV, D8) plus either 1) 5-FU (200 mg/m2, 5-FU 200 mg/m2 IV bolus, 5-FU 1000mg/m2 continuous IV infusion D1) or 2) gemcitabine (1000 mg/m2 IV, D1), or 3) irinotecan (125 mg/m2 IV, D1), q3w, until disease progression/unsurvivable toxicity. The primary endpoint was safety. Secondary objectives included tumor response & evaluation for reovirus replication/immune analysis.

Results: 11 pts were enrolled with pelareorep, pembrolizumab and gem (n = 6), 5-FU (n = 3), or 5-FU (n = 2). Most common grade 1 or 2 TEAEs include: fever (73%), headache (55%), diaphoresis (36%), fatigue (27%), abdominal pain (27%), vomiting (27%) and neutropenia (27%). One pt (gem arm), transient Gr 2 increased transaminases was reported on two occasions. Grade 3 or 4 TEAEs occurred in 8 pts (73%): abdominal pain, anemia, arthralgias, biliary obstruction, chills, DVT, diarrhea, fever, hyperglycemia, leukopenia, myalgias, nausea, neutropenia, pulmonary embolus, urinary tract infection and vomiting. Of the 6 efficacy evaluable pts, one had Pr (17.4 m duration) and 5 SD (lasting 126 and 277 days). Nine deaths occurred in pts. On-treatment biopsy show reovirus infection in cancer cells and immune infiltrates.

Conclusions: The combination therapy showed manageable safety profiles and antitumor activity in previously treated MAP pts. Further evaluation of anti-tumor activity of pelareorep and anti-PO-1 antibody ± chemotherapy combos is planned.

Table 1. Baseline Characteristics

![Table 1. Baseline Characteristics](image)

Table 2. Treatment Emergent Adverse Events Occurring in ≥ 10% Patients

<table>
<thead>
<tr>
<th>Event</th>
<th>Arm 1 (n=3)</th>
<th>Arm 2 (n=6)</th>
<th>Arm 3 (n=2)</th>
<th>Total (n=11)</th>
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<tbody>
<tr>
<td>Anemia</td>
<td>2 (67%)</td>
<td>1 (17%)</td>
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<td>3 (27%)</td>
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<tr>
<td>Neutropenia</td>
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Figure 3. On-treatment biopsy

In situ hybridization and IHC analysis showing reovirus RNA (blue staining) and reovirus protein / infiltration (brown staining). Note that the majority of cancer cells show strong reoviral RNA proliferation which is absent in the adjacent benign cells.

Figure 4. Baseline and on-treatment biopsies (pt. 002)

show reovirus infection in tumor cells, infiltration by CD8+ T cells and caspase activation as evaluated by IHC (brown staining) after combination therapy

Figure 2. Swimmer plot

In one pt (gem arm), transient Gr 2 increased transaminases was reported on two occasions. Grade 3 or 4 TEAEs occurred in 8 pts (73%) as mentioned in the abstract, with only one event of each.

Figure 2. Efficacy

- Of 6 efficacy evaluable pts, one achieved partial response (PR) 197 days after the start of therapy that has lasted 17.4 months.
- Two additional patients achieved stable disease (SD) 57 and 69 days on therapy, lasting 277 and 126 days, respectively.
- Nine patients have died secondary to PD.

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<table>
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Conclusion

The combination therapy showed manageable safety profiles and antitumor activity in previously treated MAP pts. Further evaluation of anti-tumor activity of pelareorep and anti-PO-1 antibody ± chemotherapy combos is planned.


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