A Phase 1 Study of Oncolytic Immunotherapy of Metastatic Neuroendocrine Tumours using Intralresal Rose Bengal Disodium: Cohort 1 Results

**Background**

Neuroendocrine tumours (NET) associated with the gastrointestinal tract are frequently indolent but troublesome as a result of endocrine secretory properties and a propensity for metastasis to the liver, nodes and lungs. Metastatic NET (mNET) located in the midgut and liver often secrete vasoactive products, giving rise to “Carcinoid Syndrome” (e.g., flushing, diarrhoea, wheezing, abdominal cramps and periperal oedema). These symptoms are the focus of a validated quality of life instrument (EORTC QLQ-GI-NET21). Chromogranin A (CgA) is a sensitive serum biomarker for disseminated disease, while somatostatin receptor (SSTR) expression by 68Ga-DOTATATE PET provides a means for radiologic assessment of tumour viability.

Treatment options for mNET include surgical resection, chemoa Reduction of biochemical markers and symptoms resulting from percutaneous interventionalpiration of PV-10 in 7 subjects with progressive mNET with hepatic lesions not amenable to resection or other potentially curative therapy. Target lesion(s) are defined by the interventional radiologist and must be 1.0 - 3.9 cm in longest diameter. There are two sequential dose escalation cohorts (up to 6 subjects in each) based on number of discrete interventions. Cohort 1 subjects receive PV-10 to a single hepatic lesion per treatment cycle, and can receive PV-10 to additional un.injected hepatic lesions 26 weeks after prior injection. Cohort 2 subjects may receive injection of multiple lesions per treatment cycle.

**Methods**

This single-centre phase 1 study (protocol PV-10-001, ClinicalTrials.gov identifier NCT02693067) is evaluating the safety, tolerability, and reduction of biochemical markers and symptoms resulting from percutaneous interventional aspiration of PV-10 in 12 subjects with progressive mNET with hepatic lesions not amenable to resection or other potentially curative therapy. Target lesion(s) are defined by the interventional radiologist and must be 1.0 - 3.9 cm in longest diameter. There are two sequential dose escalation cohorts (up to 6 subjects in each) based on number of discrete interventions. Cohort 1 subjects receive PV-10 to a single hepatic lesion per treatment cycle, and can receive PV-10 to additional uninjectect hepatic lesions 26 weeks after prior injection. Cohort 2 subjects may receive injection of multiple lesions per treatment cycle.

**Cohort Number of Subjects PV-10 Dose per Lesion Volume Maximum Number of Lesions Injected per Treatment Cycle Maximum PV-10 Dose per Treatment Cycle**

<table>
<thead>
<tr>
<th>Number</th>
<th>Subjects</th>
<th>PV-10 Dose per Lesion Volume</th>
<th>Maximum Number of Lesions Injected per Treatment Cycle</th>
<th>Maximum PV-10 Dose per Treatment Cycle</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6</td>
<td>0.5 mL/cm²</td>
<td>1 in a single segment</td>
<td>15 mL</td>
</tr>
<tr>
<td>2</td>
<td>6</td>
<td>0.5 mL/cm²</td>
<td>1 or more</td>
<td>15 mL</td>
</tr>
</tbody>
</table>

Disease evaluations are performed at screening, week 6, and months 3 and 6 after PV-10 injection.

**The Primary Endpoint:** Safety

- Safety will be established in Cohort 1 if no more than 1 of the 6 subjects experiences a dose-limiting toxicity (DLT), defined as onset of any CTCAE Grade 3 or greater non-haematological (excluding fatigue) or Grade 4 haematological toxicity within 28 days of PV-10 administration that is persistent for 14 days or longer. If 2 or more subjects experience a DLT, then PV-10 injection will be judged to be intolerable.

**Secondary Endpoints:**

- Objective response rate (ORR) of injected Target and bystander lesions; ORR assessed by contrast-enhanced CT.
- Target lesion SSR expression by 68Ga-DOTATATE PET; standardised uptake value (SUV) used as a surrogate for tumour viability.
- Changes in biochemical response (serum biomarker CgA).
- Symptom assessment using patient-reported outcome (QLQ-GI-NET21).
- Changes in peripheral blood mononuclear cells (PBMCs) vs baseline.

**Subject Characteristics**

Cohort 1 (N = 6) has Full Enrolled:

- 4 of 6 subjects male
- Median age 65 yrs (range 47-72) Primary site: small intestine (N = 3), pancreas (N = 2), caecal (N = 1)
- Grade: Gd3 (N = 5), Gd2 (N = 1)
- All subjects received prior SSA and PRRT
- Median CgA at baseline was 645 (range 30-2819)

**Results: Clinical and Biomarker Outcomes**

**Study Treatments and Safety:**

- To date 1 subject in Cohort 1 has received 4 PV-10 treatment cycles, 1 has received 2 cycles, and 4 have received a single cycle
- Median dose/cycle = 2.1 mL, PV-10, range = 1.0 – 5.8 mL
- Toxicity has been acceptable, including pain post-procedure, carcinoid flare and nausea
- LFTs have remained stable

**Clinical and Biomarker Outcomes:**

- Overall QOL score was stable for 5 of 6 subjects
- CgA response: 5 stable, 1 progression
- One subject with “carcinoid pellagra” had rash resolution
- PBMC data not currently analysed (insufficient data at cutoff date)

**Results: CT and PET/CT Assessment**

Roselle bengal disodium is a tetraiodinated fluorescein derivative (4,5,6,7-tetrahydrochloro-2',4',5',7'-tetraiodofluorescein disodium). The presence of 4 iodides facilitates visualization on CT during administration and follow-up.

**Results: Assessment of Change is SST**

Maximum intensity projection (MIP) illustrates local and systemic response.

**Results: Objective Response**

**Objective Response (Cohort 1):**

- ORR in injected lesions is 50% (progression in 1 subject), with overall disease control of 83%
- Response follow-up is ongoing for 3 of 6 subjects in Cohort 1

**Conclusions:**

- PV-10 elicited no safety concerns in hepatic mNET, with a safety profile consistent with percutaneous interventional delivery to other hepatic malignancies (13,14)
- PV-10 is readily imaged during administration and follow-up
- Encouraging single-agent activity is evident in injected lesions
- PV-10 may yield systemic disease control through T cell activation
- Combination of PV-10 with checkpoint inhibition (CI) may overcome lack of CI activity in NET [1] (an immunologically “cold” class [2])
- Enrolment to Cohort 2 of the single-agent study is underway (2 of 6 subjects have received at least one cycle of PV-10 in Cohort 2)
- Future development options include:
  - Expansion of current single-agent study to open a phase 1 expansion cohort at multiple centres in AUS and USA
  - Initiation of a phase 2 combination study with anti-PD-1 or anti-PD-L1 antibodies (pharma partner needed for CI supply and co-sponsorship)
- Academic co-sponsorship with regional or global consortium

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