A Phase 1 Study of Oncolytic Immunotherapy of Metastatic Neuroendocrine Tumours using Intralesional Rose Bengal Disodium

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Background

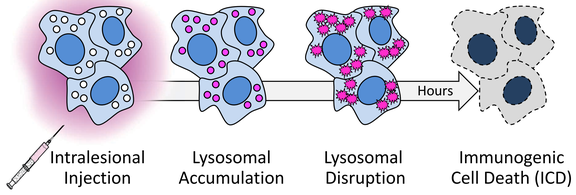
Neuroendocrine tumours (NET) associated with the gastrointestinal tract are frequently indolent but troublesome as a result of endocrine secretory properties and a propensity for metastasis to the liver, nodes and lungs.

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 peripheral oedema). These symptoms are the focus of the 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 ^{68}Ga-DOTATATE PET provides a means for radiologic assessment of tumour viability.

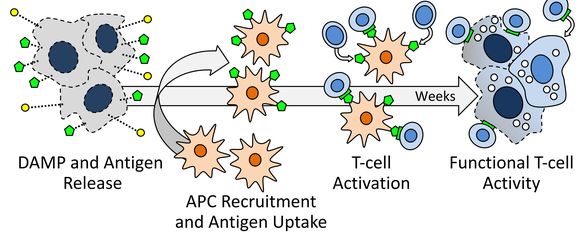
Treatment options for mNET include surgical resection, chemoablation, and systemic somatostatin analogues (e.g., octreotide, lantreotide) or radio-labelled analogues (e.g., Lutate/Lutathera, ^{177}Lu DOTA-octreotate). However, there remains a need for additional options for mNET patients.

A paradigm shift in anti-cancer therapy has occurred over the last decade with the introduction of immunotherapy treatments. Intralesional rose bengal disodium (PV-10) is an oncolytic immunotherapy [1-5] undergoing clinical development for solid tumours (e.g., cutaneous melanoma, metastatic uveal melanoma, hepatocellular carcinoma) [6-8].

Primary Oncolysis



Secondary Adaptive Immunity



Trial Design

This single-centre phase 1 study (protocol **PV-10-NET-01**, ClinicalTrials.gov Identifier **NCT02693067**) is evaluating safety, tolerability and reduction of biochemical markers and symptoms resulting from percutaneous intralesional administration of PV-10 in up to 12 subjects with mNET of the liver not amenable to resection or other potentially curative therapy.

Target Lesion(s) will be defined by the interventional radiologist (uni-dimensionally measurable with longest diameter of 1.0 to 3.9 cm) and will receive PV-10 via percutaneous injection under CT or ultrasound guidance.

Subjects will be divided into two sequential dose escalation cohorts (up to 6 subjects in each) based on number of interventions per treatment cycle:

Cohort	Number of Subjects	PV-10 Dose per Lesion Volume	Maximum Number of Target Lesions Injected per Subject per Treatment Cycle	Maximum PV-10 Dose per Treatment Cycle
1	6	0.5 mL / cm^3	1 in a single segment	15 mL
2	6	0.5 mL / cm^3	1 or more	15 mL

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.

Subjects with tumour burden that cannot be injected fully in the initial treatment cycle may receive repeat administration to additional injectable tumour(s) after 6 or more weeks follow-up.

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

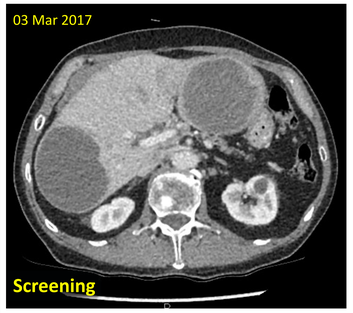
The primary endpoint is safety. Secondary endpoints include objective response rate (ORR), target lesion somatostatin receptor (SSTR) expression and biochemical response. ORR is assessed by contrast enhanced CT and ^{68}Ga-DOTATATE PET standardised uptake value (SUV) with SSTR expression used as a surrogate for tumour viability.

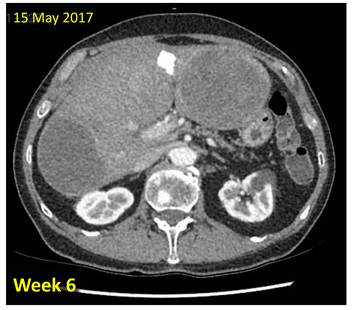
In addition to characterizing direct effect of PV-10 in injected lesions, response of non-injected bystander lesions is evaluated by CT and PET to characterize potential systemic benefit. Integration of patient-reported outcome (QLQ-GI.NET21), serum biomarker (CgA) and objective response (PET) data will allow testing of concordance between independent indicators of clinical benefit.

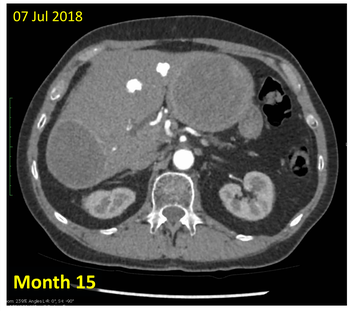
Administration and Follow-up

Rose bengal disodium is a tetraiodinated fluorescein derivative (4,5,6,7-tetrachloro-2',4',5',7'-tetraiodofluorescein disodium).

The presence of 4 iodides facilitates visualization of PV-10 on CT during administration and follow-up.







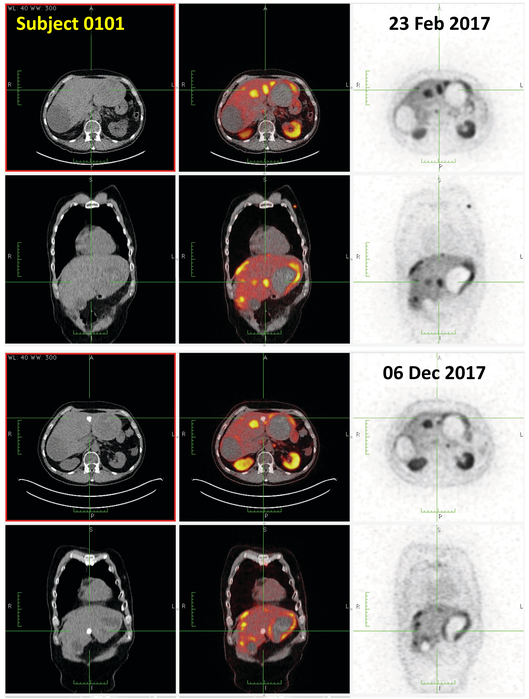
Subject 0101: Male age 63, multifocal hepatic mNETs (small intestine primary) with symptomatic progression on 30 mg Lutate (^{177}Lu DOTA-octreotate).

Follow-up at 6 weeks and 15 months after injection of PV-10 to a mNET tumour illustrates visualization of PV-10 over time (middle and bottom images).

Subsequently injected tumour adjacent to initial injection site evident at month 15 (bottom image).

^{68}Ga-DOTATATE PET/CT

PET/CT allows evaluation of concordance between injected tumours and local and systemic response.



Trail Status

- **CURRENTLY RECRUITING PATIENTS INTO COHORT 2**
- **INVESTIGATORS NEEDED FOR PHASE 2**

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1. Wachter et al., SPIE 4620, 143, 2002 (lysosomal accumulation and rupture in tissue culture)
2. Thompson et al., Mel Res 18, 405, 2008 (phase 1 study of PV-10 in metastatic melanoma)
3. Toomey et al., PLoS One 8, e68561, 2013 (tumour-specific immune response in mice)
4. Liu et al., Oncotarget 7, 37893, 2016 (DAMPs, DC recruitment/activation, T-cell activation in mouse and man)
5. Qin et al., Cell Death and Disease 8, e2584, 2017 (immunogenic cell death in colon cancer)
6. Thompson et al., J Surg Oncol 22, 2135, 2015 (phase 2 study of PV-10 in metastatic melanoma)
7. Foote et al., J Surg Oncol 115, 891, 2017 (phase 2 study of PV-10 and hypofractionated radiation in metastatic melanoma)
8. Goldfarb et al., CIO 2017, abstract 15831 (phase 1 basket study of percutaneous PV-10 in hepatic tumors)