Phase 1a open-label, non-randomized, multi-centre clinical trial of intratumoral IVX037 in patients with advanced microsatellite stable (MSS) colorectal, gastroesophageal or ovarian cancer: trial in progress

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BACKGROUND

- Oncolytic viruses have emerged as promising therapeutic agents that selectively infect and destroy cancer cells while synergizing with checkpoint inhibitors to increase immunotherapy efficacy.
- IVX037 is a novel bio-selected, receptor targeted, non-genetically modified, naturally occurring oncolytic strain of a human enteric picornavirus.
- It is a non-enveloped, single-positive-stranded RNA virus with a capsid diameter of ~25nm.
- IVX037 challenge can induce selective *in vitro* tumor cell lytic infection via specific viral capsid cellular receptor interactions in cell cultures of human colorectal, gastric and ovarian cancers.
- Significant anti-tumor activity was displayed by a single intratumoral injection of IVX037 in human xenografts of microsatellite stable (MSS) colorectal ***(Figure 1),*** gastric and ovarian cancers in SCID mice.
- *In vivo* human MSS colorectal cancer xenograft studies in mice, revealed that intratumoral administration of IVX037 induced elevated levels of γ-INF response genes (CXCL10, RIG-I) and up-regulated expression of a key immune-checkpoint molecule, PD-L1 ***(Figure 2),*** indicating an inflammation phenotype within the treated tumor microenvironment (TME) .
- The induction of a virally inflamed TME is suggested to potentially allow increased migration of anti-tumor lymphocytes both within injected and distant lesions and elevated levels of cellular targets for immune checkpoint therapies.
- Increased serum levels CXCL10 and CCL22 in melanoma patients administered with another RNA oncolytic virus, V927 in combination with pembrolizumab, were associated with responses suggesting viral replication contributes to antitumor immunity (*Silk AW, et al, 2023* Cancer Immunol Immunother; 72(6):1405-1415).

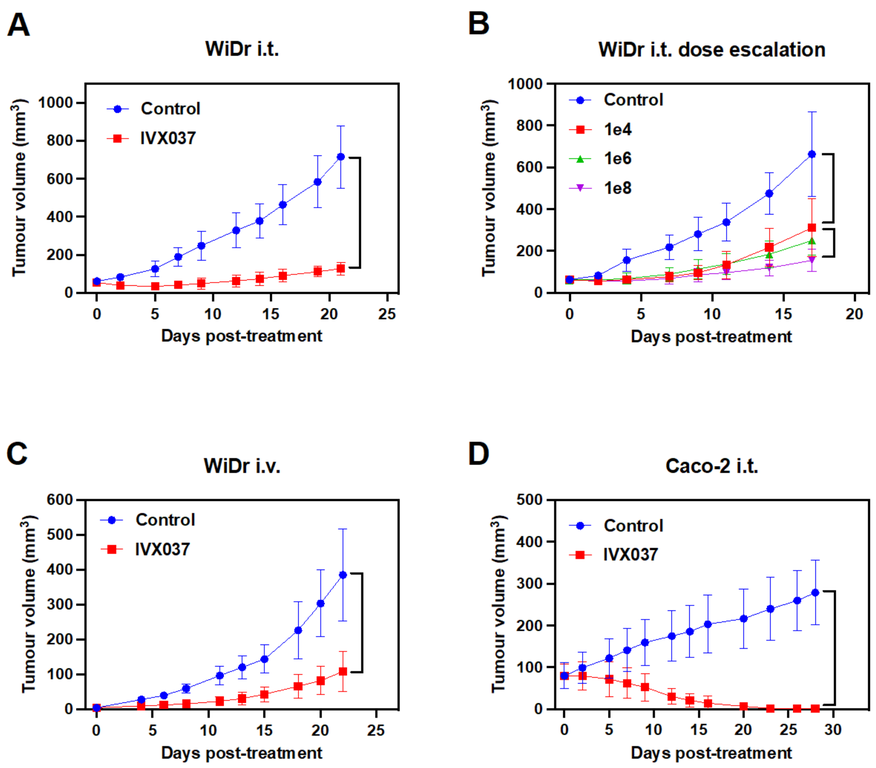

Figure 1. IVX037 infects and replicates in human colorectal cancer xenografts resulting in tumor growth inhibition. (*A) A single injection of IVX037 (1x10[8] $TCID_{50}$) was administered intratumorally (i.t) into WiDr tumor xenografts. (B) IVX037 at escalating doses (1 × 10[4], 1 × 10[6], 1 × 10[8] $TCID_{50}$) was injected intratumorally to the WiDr tumor xenografts. (C) Mice bearing WiDr tumor xenografts were treated with four intravenous (i.v) infusions of IVX037 spaced three to four days apart. (D) A single injection of IVX037 (1x10[8] $TCID_{50}$) was administered intratumorally into Caco-2 tumor xenografts. Tumor volumes were expressed as the mean ± SD (mm3). ****P < 0.0001.*

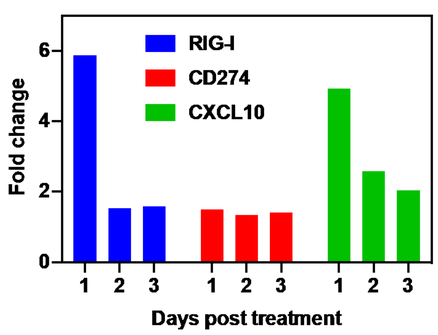

Figure 2 Expression of RIG-I, CD274 and CXCL10 at 1-, 2- and 3-day post treatment. *SCID mice were inoculated with WiDr cells. When tumors reached to an average size (approximately 50 mm3), mice were treated with virus IVX037 (n = 8 mice) or control formulation buffer (n = 6 mice) on the day 0. Mice were sacrificed at 1, 2, and 3-day post treatment. Tumors were collected and RNA was extracted. Expression of RIG-I, CD274 and CXCL10 was measured using RT-PCR and calculated as a fold change.*

METHODS

- This is a Phase 1a, first-in-human, open-label, non-randomized, multi-centre clinical trial of intratumoral IVX037 in patients with advanced MSS colorectal , gastroesophageal or ovarian cancer.
- ***Inclusion criteria:*** Patients (pts) must have one injectable tumour of liver/nodal/peritoneal disease.
- ***Exclusion criteria:*** Candidate for hepatic surgery or locoregional therapy for liver or other lesions. Clinically significant ascites (Grade ≥2), continuous systemic treatment with either corticosteroids (> 10 mg daily).
- ***Intervention:*** Pts will be sequentially enrolled into 3 dose escalation cohorts to receive 1 (n=3 pts), 2 (n=3 pts) or up to 7 doses permitted at Investigator discretion in absence of DLTs' (n=15) of up to 3 x 10[8] $TCID_{50}$ of IVX037 doses for Cohort 3 intratumorally, administered on Days 1, 15, 29, 43, 57, 71 and 85, as applicable, ***Figure 3.***
- ***Primary objective:*** to determine the feasibility, safety and tolerability of intratumoral IVX037 including the incidence of dose-limiting toxicities (DLT).
- ***Secondary objectives:*** to assess the maximum tolerated dose (MTD) of IVX037, administered as either 1, 2 or 3 injections per lesion. Tumor response will be assessed using RECIST 1.1, with the first response assessment occurring at Day 50.
- ***Exploratory objectives:*** Several biomarker effects of IVX037 administration in peripheral blood and tumor tissue addressing tumor infiltrating lymphocytes and cellular target expression levels for immune checkpoint therapies will be assessed.

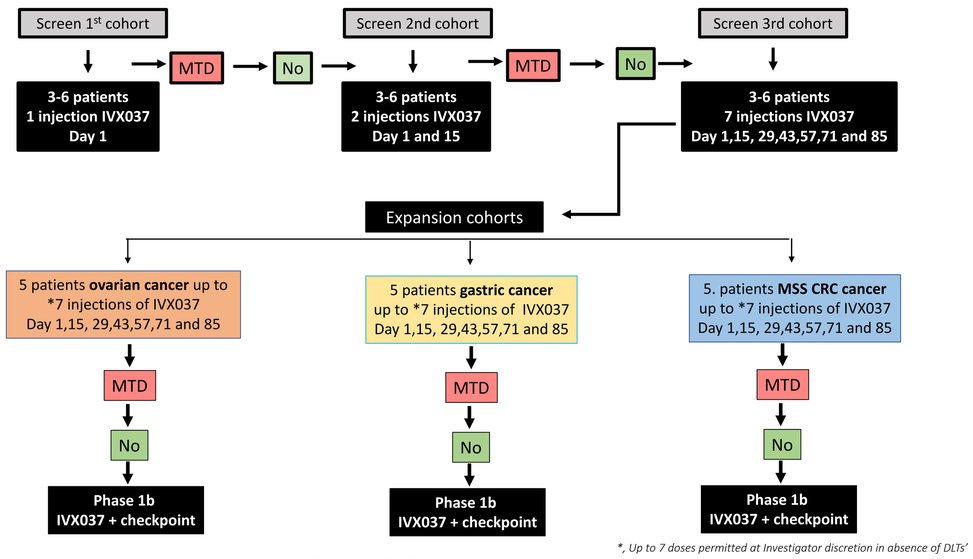

Figure 3. Phase 1a/b trial schema.

PROGRESS TO DATE

- Patient recruitment commenced in April 2023, with currently 8 pts enrolled. IVX037 dosing in Cohorts 1 and 2 is complete, with Cohort 3 dosing ongoing.
- To date IVX037 intralesional administration has been generally well tolerated, with all patients exhibiting some level of systemic exposure immediately following injection (***Figure 4A***), with no dose-limiting toxicities observed. Mild flu-like reactions after injection (fatigue, chills, rigors, injection site discomfort) observed.
- IVX037 has been successfully administered to liver, lymph node and abdominal metastases.
- Currently all patients have developed serum neutralising anti-IVX037 antibodies by Day 15 post-viral administration (***Figure 4B***).
- Preliminary serum biomarker analysis has indicated early signs of IVX037 induction of potentially beneficial inflammatory cytokines/chemokines, such as CXCL10 (***Figure 4C***).
- Recruitment is ongoing and Phase 1b in combination with immune checkpoint blockade is planned.

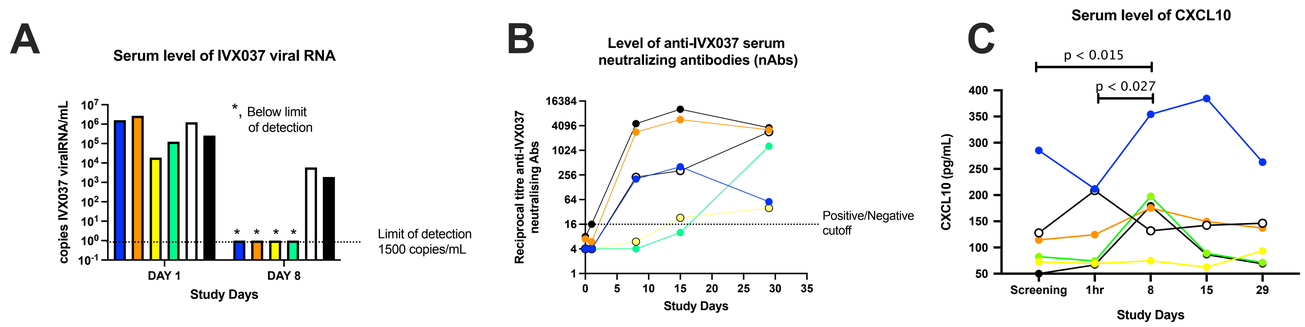

Figure 4 (A) Patient serum levels of IVX037 viral RNA. *IVX037 viral levels were determined using semi-quantitative RT-qPCR.* ***(B) Patient serum levels of neutralizing antibodies (nAbs) post IVX037 administration. (C) Patient serum CXCL10 levels.*** *CXCL10 levels were determined using a multi-plex flow cytometry assay. Statistical analysis utilised a paired sample "t-test " technique.*

SITC 2023, November 3-5, San Diego USA. *Corresponding author: jia.liu@svha.org.au*
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