Phase 1a/b open-label, non-randomized, multi-centre clinical trial of intratumoral IVX037 monotherapy and in combination with anti-PD-1 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, non-enveloped, single-positive-stranded RNA virus. It is an oncolytic strain of a naturally occurring human enteric picornavirus.
- IVX037 challenge highly inflames "cold" tumors with current low responsiveness to immune checkpoint inhibitors, stimulating anti-tumor immune response ***(Figure 1***).
- The induction of a virally inflamed tumor microenvironment (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.

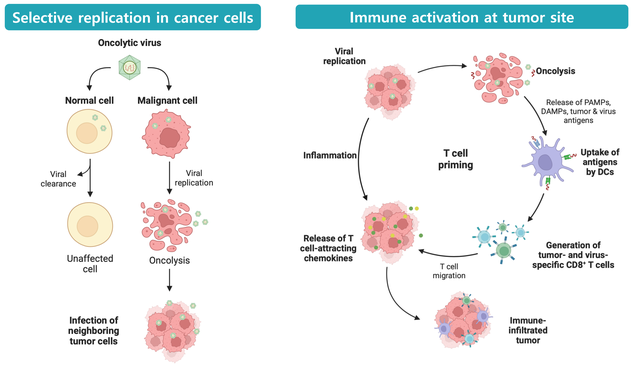

Figure 1 Selective replication in cancer cells and immune activation at tumor site (Adapted from Potential of TGF-β Inhibition and Oncolytic Viruses. Trends Immunol. 2020 May;41(5):406-420.)

- Significant anti-tumor activity was displayed by a single intratumoral injection of IVX037 in human xenografts of microsatellite stable (MSS) colorectal ***(Figure 2),*** 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 g-INF response genes (CXCL10, RIG-I) and up-regulated expression of a key immune-checkpoint molecule, PD-L1 indicating an inflammation phenotype within the treated tumor microenvironment (TME).
- 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 *)*.

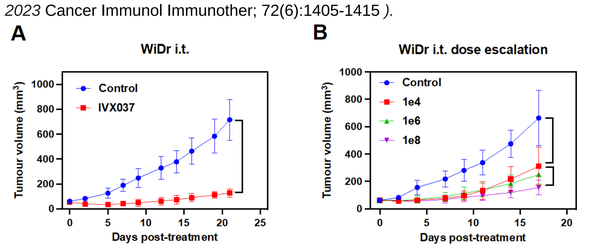

Figure 2. IVX037 infects and replicates in human colorectal cancer xenografts resulting in tumor growth inhibition. (*A) A single injection of IVX037 (1x10[8] $TCID_{50}$) was administered intratumorally (i.t) into WiDr tumor xenografts. (B) IVX037 at escalating doses (1 × 10[4], 1 × 10[6], 1 × 10[8] $TCID_{50}$) was injected intratumorally to the WiDr tumor xenografts.*

STUDY DESIGN

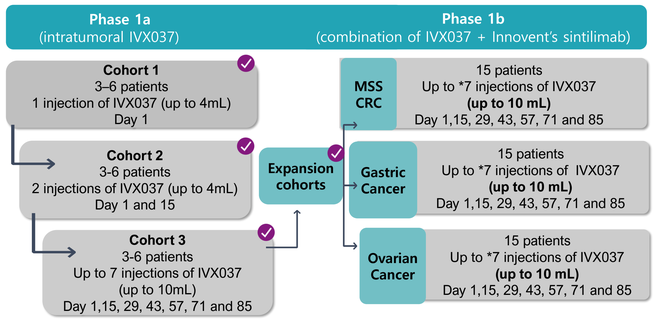

Figure 3. Phase 1a/b trial schema.

CASE STUDIES – monotherapy participants

MSS CRC CASE STUDY 1 – exceptional responder

2017	• **Aug** laparoscopic anterior resection for T4N0M0 (MSS) recto-sigmoid adenocarcinoma • **Aug—Jan 2018** adjuvant capecitabine
2019	• **Feb** recurrence in omentum and liver • **Apr-Dex 2019** FOLFOX → cytoreductive surgery + HIPEC → FOLFOX
2020	• **Jan** recurrence in peritoneum and abdominal wall • **Feb-Jan 2023** capecitabine and bevacizumab – best response: SD
2023	• **Jan** abdominal pain • **Feb** radiotherapy RUQ mass • **May** worsening pain RIF mass

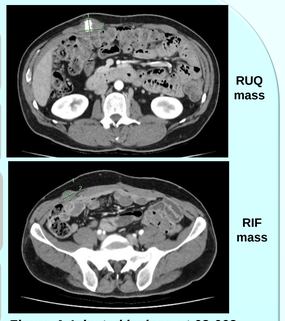

Figure 4. Injected lesions pt 02-003.

55yo white male, pt ID 02-003, previously healthy

- Consent and screen for CP-IVX001 in June 2023 cohort 1
- CT June 2023: 2 injected palpable lesions represent 100% of disease burden, ***Figure 4***
- Target lesion dimensions 23x22mm
- Both lesions injected with IVX037 - dosing volume: TL 2 ml; NTL 2 ml
- First dose in June 2023, last dose in Dec 23 – trial completed with 5 doses received
- Biopsy of both lesions shows scant cancer cells in RUQ mass, CR in RIF mass; PET-CT shows no further metastatic spread, ***Figure 5***
- Imaging response (RECIST 1.1): stable disease; corresponding decrease in CEA levels, ***Figure 6***
- **Patient did not require further treatment for 15 months since trial initiation and 8 months since completion of trial** => indicative of systemic response and abscopal effect

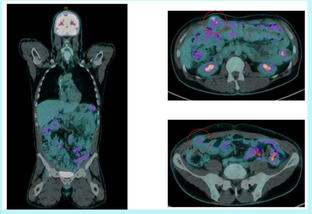

Figure 5. PET-CT scan shows no further metastatic spread.

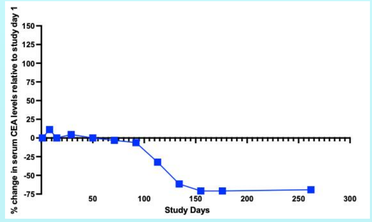

Figure 6. Percentage change of serum CEA levels to baseline (Preliminary data)

MSS CRC CASE STUDY 2 – positive activity in injected lesion

57yo Asian female, pt ID 02-004

- Consent and screen for CP-IVX001 in July 2023, cohort 2
- Original diagnosis of caecal carcinoma in Aug 2020; T3 N2 M0
- Surgery followed by adjuvant chemo and further systemic therapy in a metastatic setting, RT
- CT Aug 2023: 1 injected lesion; dosing volume: TL lymph node 2 ml, total of 2 doses received
- Near response in target lesion - 24% decrease in injected lesion (25mm to 19mm) ***Figure 7***; corresponding decrease in CEA levels, ***Figure 8***
- Patient came off study due to rheumatoid arthritis requiring steroids

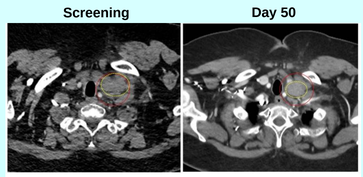

Figure 7. Decrease 24% in injected target lesion according to RECIST 1.1

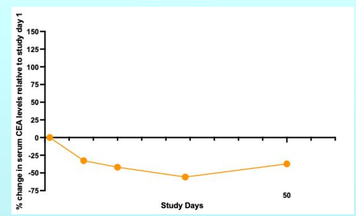

Figure 8. Percentage change of serum CEA levels to baseline

- **Promising signals** of activity in 2 late-stage MSS colorectal cancer patients
- MSS CRC participant 02-003: **complete response** in injected target lesion, confirmed by histology; absence of new metastatic disease (PET scan) for over a year with no other anticancer therapy, suggestive of IVX037 induced **abscopal** activity.

METHODS

- This is a Phase 1a/b, 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 at least one injectable tumor (up to 6.5 cm) of liver/nodal/peritoneal disease, sufficient organ function, prior immunotherapy required for GOJ/gastric cancer in Phase 1b.
- ***Exclusion criteria:*** Candidate for hepatic surgery or locoregional therapy for liver or other lesions. Clinically significant ascites (Grade ≥2), continuous systemic treatment with corticosteroids (> 10 mg daily).
- ***Intervention:*** Pts were 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=up to 15pts) of up to 7.5 x 10[8] $TCID_{50}$ of IVX037 (***Figure 9)*** doses for Cohort 3 intratumorally, administered on Days 1,15,29,43,57,71 and 85, as applicable.
- For Phase 1b, pts will be enrolled and receive up to 7 intratumoral doses of IVX037 permitted at Investigator discretion, administered on Days 1,15,29,43,57,71 and 85, as applicable.

Figure 9. IVX037 vial

- ***Primary objective:*** to determine the feasibility, safety and tolerability of intratumoral IVX037 including the incidence of dose-limiting toxicities (DLT) alone and in combination with intravenous checkpoint inhibitor
- ***Secondary objectives:*** to assess the maximum tolerated dose (MTD) of IVX037, administered as up to 7 injections per lesion. Tumor response will be assessed using RECIST 1.1, with the first response assessment occurring at Day 43.
- ***Exploratory objectives:*** Several biomarker effects of IVX037 administration in peripheral blood and tumor tissue addressing ctDNA, tumor infiltrating lymphocytes and cellular target expression levels for immune checkpoint therapies will be assessed.

PROGRESS TO DATE

- Patient recruitment commenced in April 2023.
- As of June 2024, the Phase 1a monotherapy dose escalation phase (1-3) and cohort 3 expansion has been completed with 14 pts enrolled, no DLTs have been reported and no MTD identified.
- To date IVX037 intratumoral administration has been generally well tolerated, with all patients exhibiting some level of systemic exposure immediately following injection.
- IVX037 has been successfully administered to liver, lymph node and abdominal metastases.
- Currently 83% patients have developed serum neutralising anti-IVX037 antibodies by Day 15 and 100% patients by Day 29 post-viral administration.
- Preliminary serum biomarker analysis has indicated early signs of IVX037 induction of potentially beneficial inflammatory cytokines/chemokines, such as CXCL10 showing increased levels at Day 8, providing a rationale for commencing sintilimab on Cycle 1 Day 8 (***Figure 10***).
- Recruitment is ongoing at 5 sites in Australia with more coming on through Q1 2025.
- Phase 1b in combination with immune checkpoint blockade sintilimab commenced in Sep 2024 with active participants currently on trial.
- Recruitment is ongoing in microsatellite stable (MSS) colorectal, gastroesophageal and ovarian cancer cohorts. Recruitment into hepatocellular cancer cohort will commence in 2025.
- For enquiries re eligibility and patient referrals, please see clinicaltrials.gov NCT05427487 or contact the ImmVirX Medical Director, Dr Oksana Zdanska: oksana.zdanska@immvirx.com

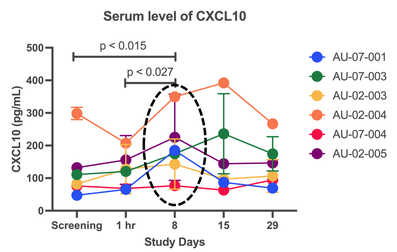

Figure 10. Promising signs of immune inflammation at Day 8

PHASE 1a MONOTHERAPY - FAVOURABLE SAFETY PROFILE

IVX037 IT administration has been well tolerated with a favorable safety profile

- No dose limiting toxicities have been observed during phase 1a

Common Grade 2 TRAEs:
- Fatigue 14.3%
- Rheumatoid arthritis 7.1%
- Injection site pain 7.1%

Common Grade 1 TRAEs:
- Injection site pain 42.9%
- Intermittent fever 35.7%
- Nausea/anorexia/chills/fatigue/abdominal tenderness 14.3%

INTRATUMORAL ADMINISTRATION

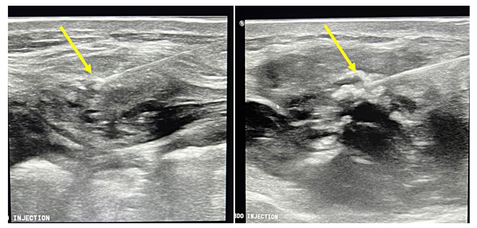

Figure 11. US-guided intratumoral delivery of IVX037

Accessing Lesions For Intratumoral Administration, *Figure 11.*

USG / CT guidance – IVX037 can be safely administered repeatedly to liver and other sites of metastases

- Preloaded syringe with IVX037 delivered to radiology rooms, 5 hours life span
- Similar outpatient procedure to biopsy and FNA – local anaesthetic +/- conscious sedation
- 20-minute procedure +/- monitoring for 2-4 hours
- Up to 5 lesions, total volume up to 10 ml (50% of total disease burden)

ImmVirX Pty Ltd would like to acknowledge the contribution of the site staff, participants and carers to this study.

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