Abstract: CT115

Phase 1b open-label, non-randomized, multi-center clinical trial of intratumoral IVX037 in combination with sintilimab (anti-PD1) in patients with advanced microsatellite stable (MSS) colorectal, ovarian or gastroesophageal cancer.

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BACKGROUND

Oncolytic viruses have emerged as promising therapeutic agents to selectively infect and destroy cancer cells while synergizing with checkpoint inhibitors to increase efficacy of immunotherapy. IVX037 is a novel bio-selected, receptor targeted, non-genetically modified, naturally occurring oncolytic strain of a human enteric RNA picornavirus. 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, ovarian and hepatocellular (HCC) cancers. Significant anti-tumor activity was displayed by intratumoral (IT) injections of IVX037 in human xenografts of microsatellite stable colorectal (MSS-CRC), gastric, HCC and ovarian cancers in SCID mice. In vivo human MSS-CRC xenograft studies in mice, revealed that IT 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, indicating an inflammation phenotype within the treated tumor microenvironment (TME). In the Phase 1a monotherapy clinical study, multiple IT administrations of IVX037 were generally well tolerated with no Gr 3 or higher TRAE's or DLTs seen. The most common Gr 1 and Gr 2 TRAE's were injection site pain (44%) and fatigue (22%), respectively. Of the 9 patients (pts) administered IVX037 in Phase 1a, one MSS, KRAS G12D mutant CRC pt achieved a biopsy confirmed complete response at day 262 after **five I**T doses. Two MSS-CRC pts displaying injected lesion reductions also exhibited decreases in serum Carcinoembryonic antigen (CEA) levels (***Figure 1***). Serum biomarker analysis highlighted IVX037-mediated induction of potentially beneficial inflammatory cytokines/chemokines (ie.CXCL10) at day 8 for future enhancement of combination Phase 1b CPI therapy (***Figure 2;*** Wong et al. AGITG ASM, 2024).

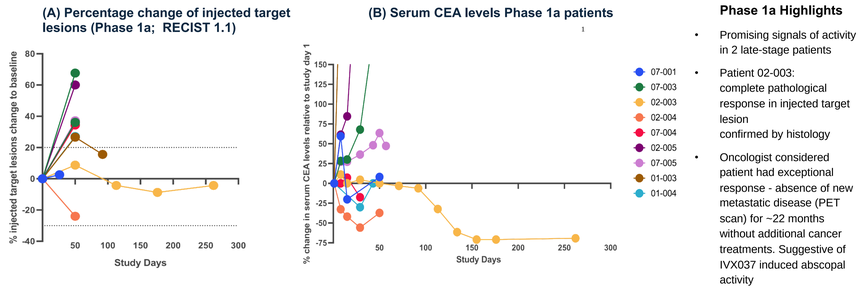


Figure 1. (A) *Percentage change (RECIST 1.1) of injected target lesions in patients from Phase 1a Cohorts 1, 2 and 3 administered intratumoral IVX037.* ***(B)*** *Serum CEA levels in patients from Phase 1a Cohorts 1, 2 and 3 administered intratumoral IVX037.*

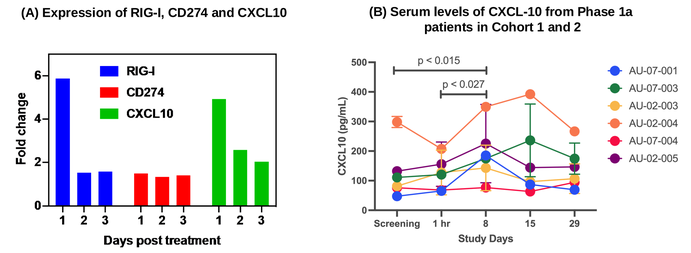
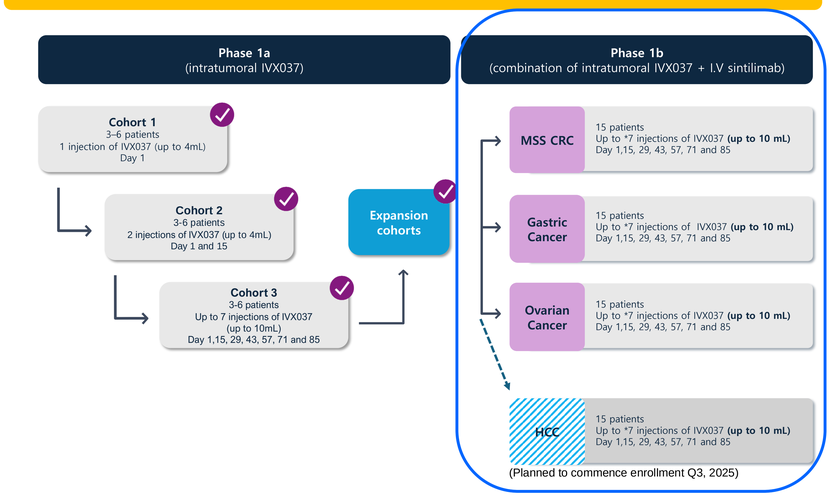


Figure 2. (A) *Expression of RIG-I, CD274 and CXCL10 at 1-, 2- and 3-day post treatment. In preclinical studies SCID mice were inoculated with WiDr (MSS-CRC) cell, when tumors reached to an average size (approximately 50 mm3), mice were treated with intratumoral IVX037 (n = 8 mice) or control formulation 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.* ***(B)*** *Serum levels of CXCL-10 (multi-plex flow cytometry) in patients from Phase 1a Cohorts 1 and 2 administered intratumoral IVX037.*

TRIAL DESIGN



This is a Phase 1b, first-in-human, open-label, non-randomized, multi-center clinical trial of IT IVX037 in combination with an intravenous (IV) immune checkpoint inhibitor, sintilimab (anti-PD1) in patients with advanced MSS-CRC, gastroesophageal or ovarian cancer. Pts must have at least one injectable tumor. A total of 45 participants (15 from each of the three tumor types) will be enrolled and receive IT doses of IVX037 administered Q2W on Days 1,15, 29,43,57,71 and 85 at dose of up to 7.5 x 10^8 $TCID_{50}$ (a dosage level deemed safe during the Phase 1a study), sintilimab administration will commence on Study Day 8 and be administered Q3W at 200 mg/dose through to Study Day 344. The primary objective is to determine the feasibility, safety and tolerability of IT IVX037 in combination with sintilimab including the incidence of dose-limiting toxicities (DLT) developing within 21 days after the third dose of IVX037 and two doses of sintilimab. Tumor response will be assessed using iRECIST, with the first response assessment occurring at Day 43. 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. ctDNA levels will also be monitored.

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KEY ELIGIBILITY CRITERIA

Inclusion:

1. Has either a histologically confirmed advanced MSS colorectal, GOJ/gastric, ovarian cancer that has progressed or is not suitable for standard of care systemic therapies. Participants with colorectal cancer must have either a primary tumor or a biopsy of a metastatic tumor which has been shown to lack microsatellite instability (by PCR) or to have normal expression of mismatch repair enzymes (by immunohistochemistry).
2. Progressed on or after at least one prior line of systemic therapy and must not have had more than 3 prior lines. Participants with gastroesophageal cancer must have failed prior treatment with an immune checkpoint inhibitor.
3. Has at least one injectable tumor that meets RECIST1.1 criteria to be designated as a target lesion, and is:
   I. a liver lesion 1.0 to 6.5 cm (longest diameter) meeting RECIST criteria on baseline CT scan or MRI and suitable for injection under CT or ultrasound guidance, and participant has an estimated total tumor burden of disease < 1/3 of liver volume based on CT or MRI imaging, or
   II. A measurable lymph node, i.e., with a short axis diameter (SAD) of 1.5 cm to 6.5 cm, or
   III. Other solid tumor with a longitudinal diameter 1.0 cm to 6.5 cm.
   IV. No other lesions (including non-injected lesions) greater than 6.5 cm (longest diameter).
4. Has a performance status of 0 or 1 on the Eastern Cooperative Oncology Group (ECOG) performance scale.

Exclusion :

1. The potential participant is deemed to be a candidate for hepatic surgery or locoregional therapy for liver lesions with curative intent or requires other systemic anti-cancer therapy.
2. The participant has clinically significant ascites (Grade ≥2).
3. The participant requires continuous systemic treatment with either corticosteroids (>10 mg daily prednisone or equivalent) or other immunosuppressive medications within 4 weeks prior to the first dose of study treatment.
4. Participants with bleeding diathesis due to underlying medical conditions or the use of anticoagulation medications that is unable to be reversed by medical treatment.
5. Participants with tumors that lie close to an airway, major blood vessel or spinal cord, which, in the opinion of the Investigator, could cause occlusion, compression, or erosion of the vital structures

KEY TRIAL ENDPOINTS

Primary

- To assess the safety and efficacy of intratumoral IVX037 in combination with an intravenous immune checkpoint inhibitor when administered to patients with advanced colorectal, ovarian, gastric and HCC cancers.

Secondary

- To make a preliminary assessment of antitumor activity of IVX037 when administered intratumorally to patients with advanced colorectal, ovarian, gastric or HCC cancers, in combination with an intravenous immune checkpoint inhibitor.

Exploratory

- To describe the effects of IVX037 on measures of immune activation in advanced colorectal, ovarian, gastric or HCC cancers.
- Changes in CEA (CRC, gastric, HCC cancer), CA125 (ovarian cancer only), CA19-9 (CRC, gastric, ovarian, HCC cancer), AFP (HCC), plasma levels of various cytokines and chemokines, and ctDNA.

PROGRESS TO DATE

- Phase 1b patient recruitment commenced in October 2024.
- Currently 4 MSS-CRC patients, 1 gastroesophageal patient, 1 ovarian cancer patient enrolled.
- No DLTs have been reported and no MTD identified.
- The Phase 1b trial is continuing as planned.
- Clinical Trial identifier: NCT05427487

Study sponsor
This study is sponsored by ImmVirX Pty Ltd (Newcastle, NSW, Australia), in collaboration with Innovent Biologics (Suzhou) Co. Ltd.

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