Abstract: 882eP

Phase I Study of Intratumoural (IT) IVX037, a Novel CD55-Targeted Oncolytic RNA Virus, in Advanced Microsatellite Stable (MSS) Colorectal Cancer (CRC): Serum Biomarkers, Viral Kinetics, and KRAS Mutation Analysis.

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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 bioselected, non-genetically modified oncolytic human picornavirus virus that targets CD55, a complement regulatory protein frequently overexpressed in CRC, especially in tumours with KRAS/BRAF mutations. IVX037 challenge can induce selective *in vitro* tumour cell lytic infection and multicycle replication via specific viral capsid cellular receptor interactions in cell cultures of human colorectal cancers, potentially more efficiently in those bearing either KRAS or BRAF mutations ***(Figure 1***). As such we postulate that such mutations may activate the MAP kinase pathway enhancing the oncolytic activity of IVX037 by increasing viral RNA replication, virion assembly and lytic release together with potential upregulation of the viral cellular receptors CD55 and FcRn ***(Figure 3).*** 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 target lesion complete response at day 262 after five IT doses. Two MSS-CRC pts both KRAS mutated displaying injected lesion reductions (***Figure 2A***) also exhibited decreases in serum Carcinoembryonic antigen (CEA) levels (***Figure 2B***). KRAS mutations were present in 5/11 pts. Pts with KRAS-mutant tumours trended to increased reductions following injection compared to pts with wild-type KRAS (p<0.05) (***Figure 4***). Two of eleven pts displayed >50% reductions in CEA levels together with notable reductions of injected target lesions. Negative baseline levels of nAbs (<1:16) were observed in 10/11 pts with positive levels (>1:16) generated in all pts by d29. Systemic IVX037 RNA was detected in all pts 1hr post-injection, with persistence through day 8 in 5/11 pts, suggesting active viral replication. The current presentation focuses on translational and efficacy data from Phase 1a and the ongoing Phase 1b study which is investigating the feasibility, safety and tolerability of IT IVX037 in combination with sintilimab.

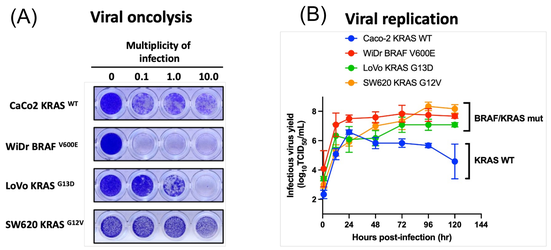


*Figure 1. In vitro IVX037 induced oncolysis and viral replication kinetics. **(A)** IVX037-mediated oncolysis in a panel of CRC cancer cells. Cells were infected with IVX037 at MOI 0.1, 1.0 and 10 $TCID_{50}$/cell and viability was measured seven days later cell staining with crystal violet. **(B)** Viral replication growth curve of IVX037 in various CRC cancer cell lines over 8 days post-infection. Cells were challenged with IVX037 at MOI = 1.0 and viral titres were determined at 0, 24, 48, 72, 96, 120 hrs post-infection.*

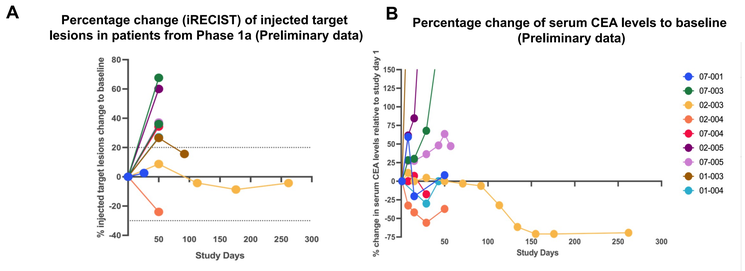


*Figure 2. **(A)** Percentage change (iRECIST) of injected target lesions in patients from Phase 1a Cohorts 1, 2 and 3 administered intratumoural IVX037. **(B)** Serum CEA levels in patients from Phase 1a Cohorts 1, 2 and 3 administered intratumoural IVX037*

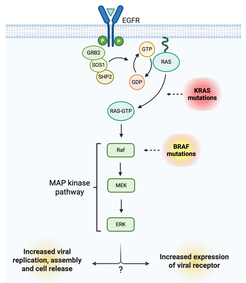


Figure 3. Schematic of the MAP kinase pathway highlighting the potential impact of KRAS and BRAF mutations in elevating the anti-tumour activity of IVX037.

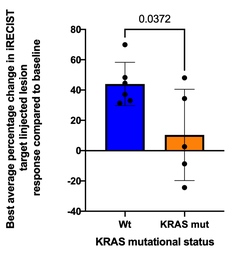
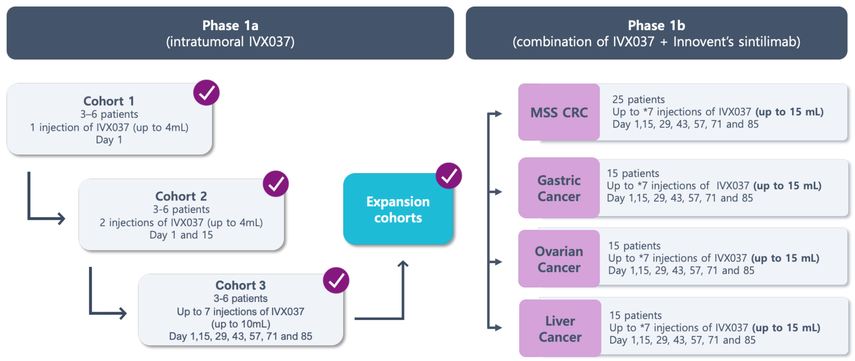


Figure 4. Best average percentage change in iRECIST target injected lesion response compared to baseline. Wt=wild type, KRAS mut = KRAS mutations. Analysis used unpaired student-t test (Preliminary data).

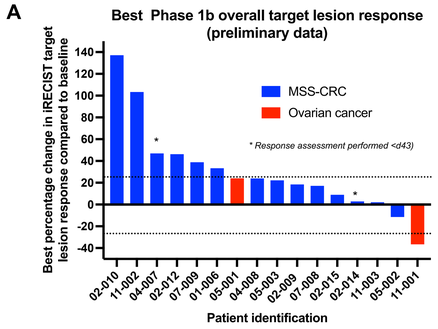
TRIAL DESIGN



The Phase 1b cohort is a 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, HCC, gastroesophageal and ovarian cancers. Patients possessed at least one injectable tumour and received IT doses of IVX037 administered 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 commenced on Study Day 8 and was administered every 3 weeks at 200 mg/dose. Tumour response was assessed using iRECIST, with the first response assessment occurring at Day 43.

RESULTS

Ongoing 1b



Phase 1b Ovarian cancer Cohort

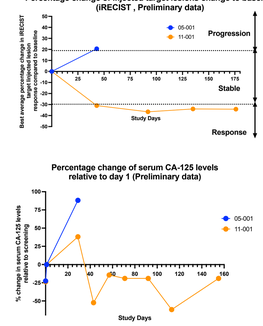


*Figure 5. **(A)** Best target lesion response in patients within the Phase 1b cohorts with either MSS-CRC or platinum resistant Ovarian cancer (iRECIST assessments were performed at d43 or greater). **(B)** Best target lesion response and CA-125 levels in patients within the Phase 1b ovarian cancer cohort.*

Phase 1b MSS-CRC Cohort

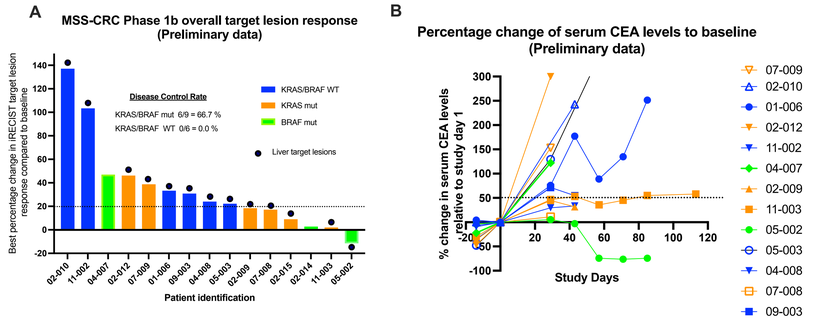


*Figure 6. **(A)** Best percentage change (iRECIST) of overall target lesion response in patients from the Phase 1b MSS-CRC Cohort. Patients were noted to possess tumour burden that was determined by molecular analysis to contain KRAS or BRAF mutations (within the MAP kinase pathway) or no KRAS or BRAF mutations (Wild type, WT). **(B)** Percentage change in serum Carcinoembryonic Antigen (CEA) levels relative to Day 1 levels. Samples for Patients 02-014 and 02-015 were not available for analysis.*

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

RESULTS cont.

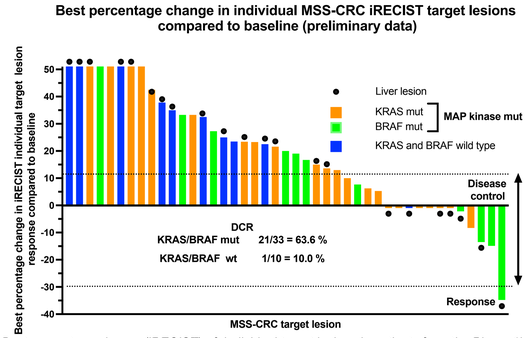
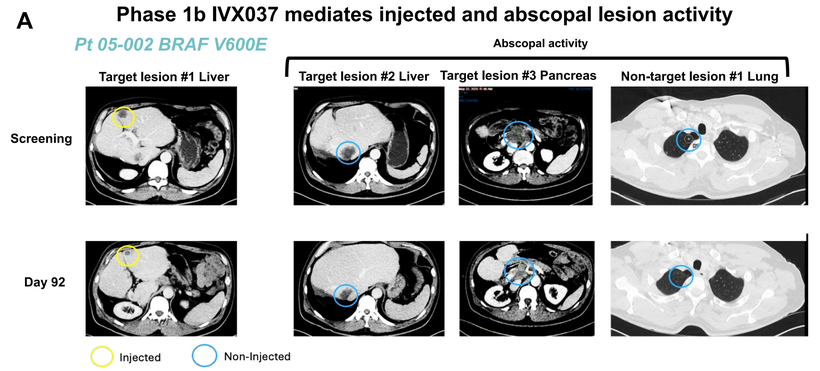


Figure 7. Best percentage change (iRECIST) of individual target lesions in patients from the Phase 1b MSS-CRC Cohort. Patients were noted to possess tumour burden that was determined by molecular analysis to contain KRAS or BRAF mutations (within the MAP kinase pathway) or no KRAS or BRAF mutations (Wild type, WT).



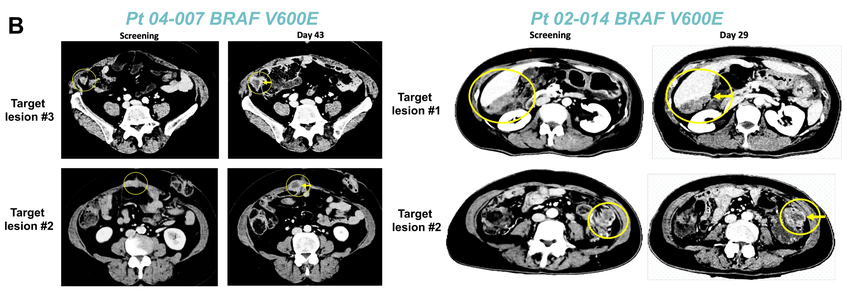


*Figure 8. **(A)** Injected and abscopal activity in a BRAF V600E MSS-CRC patient. **(B)** IVX037 induces rapid and widespread cell necrosis in abdominal lesions of two BRAF V600E MSS-CRC patients.*

CONCLUSIONS

- ***Intratumoural IVX037 demonstrated encouraging signs of biological and clinical activity in MSS-CRC as a monotherapy or in combination with sintilimab particularly in KRAS/BRAF-mutant tumours, potentially due to increased CD55 expression and viral replication from MAP kinase activation (Figures 2A and 6).***
- ***Disease control was highlighted in a numerous liver lesions, in particular, those bearing KRAS/BRAF mutations (Figure 7).***
- ***IVX037 administration induced promising abscopal activity against liver, pancreatic and lung metastases in some MSS-CRC patients (Figure 8A) together with significant reductions in serum CEA levels (Figure 6B).***
- ***IVX037 induced rapid and widespread cell necrosis in abdominal lesions of BRAF V600E MSS-CRC patients (Figure 8).***
- ***IVX037 was also active in a BRCA2 mutated ovarian cancer patient inducing a durable and ongoing PR and with notable reductions in serum CA-125 levels (Figure 5A, 5B).***
- ***Combination therapy with IVX037 and sintilimab has been generally well tolerated, with no Grade 3 or higher TRAE's for either agent.***
- ***Overall, preliminary clinical findings support further investigation of IVX037 in combination with sintilimab (anti-PD1) in ovarian cancers and MSS-CRC, especially in a KRAS/BRAF-mutant MSS-CRC enriched expansion cohort.***

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