Abstract: CT183

Phase Ib Clinical Evaluation of a Novel CD55- and FcRn-Bioselected RNA Oncolytic Virus, IVX037, Combined With Sintilimab (anti-PD-1) in Advanced Microsatellite-Stable Colorectal Cancer

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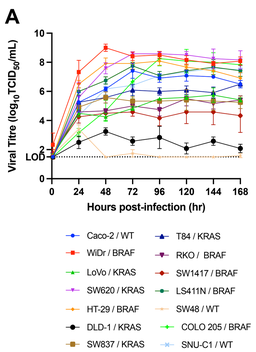
BACKGROUND

Oncolytic viruses represent a promising class of cancer therapeutics capable of selectively infecting and lysing tumor cells while enhancing responses to immune checkpoint blockade. IVX037 is a bioselected, non-genetically modified human picornavirus that targets CD55 and FcRn, receptors frequently overexpressed in colorectal cancer (CRC), particularly in tumors harboring KRAS or BRAF mutations. *In vitro* studies in human CRC cell lines demonstrate that IVX037 induces selective tumor cell lysis and supports multicycle viral replication via specific capsid–receptor interactions. Enhanced activity is observed in KRAS- and BRAF-mutant cell culture models (***Figure 1***). Mechanistically, MAPK pathway activation may potentiate viral replication, virion assembly, and lytic release, as a result of further attenuation of type I interferon anti-viral response (***Figure 2***). In the Phase 1a monotherapy arm, intratumoral (IT) administration of IVX037 was well tolerated, with no Grade ≥3 treatment-related adverse events (TRAEs) or dose-limiting toxicities. The most common Grade 1–2 TRAEs were injection site pain (44%) and fatigue (22%). Among 12 microsatellite-stable (MSS) CRC treated patients, one patient with a KRAS G12D mutation achieved a biopsy-confirmed complete response of a target lesion at day 262 following five IT doses (***Figure 3***). KRAS mutations were identified in 6/12 patients, with a trend toward greater tumor reduction in injected lesions compared to KRAS wild-type tumors (p<0.05) (***Figure 4***). This presentation highlights translational and efficacy findings from the ongoing Phase 1b trial evaluating the feasibility, safety, and tolerability of IVX037 in combination with the PD-1 inhibitor sintilimab in MSS-CRC patients.



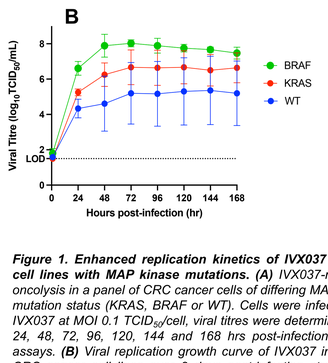


Figure 1. Enhanced replication kinetics of IVX037 in CRC cell lines with MAP kinase mutations. (A) *IVX037-mediated oncolysis in a panel of CRC cancer cells of differing MAP kinase mutation status (KRAS, BRAF or WT). Cells were infected with IVX037 at MOI 0.1 $TCID_{50}$/cell, viral titres were determined at 0, 24, 48, 72, 96, 120, 144 and 168 hrs post-infection by lytic assays.* ***(B)*** *Viral replication growth curve of IVX037 in various CRC cancer cell lines over 8 days post-infection stratified by MAP kinase mutational status (KRAS, BRAF or WT).*

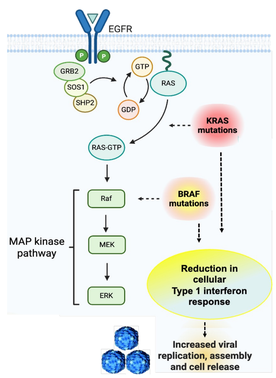
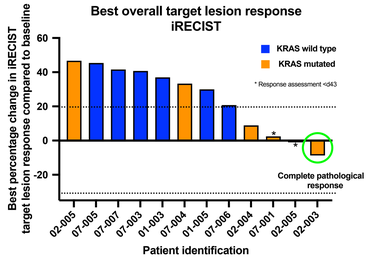


Figure 2. *Schematic of the MAP kinase pathway highlighting the potential impact of KRAS and BRAF mutations in elevating the anti-tumor activity of IVX037.*



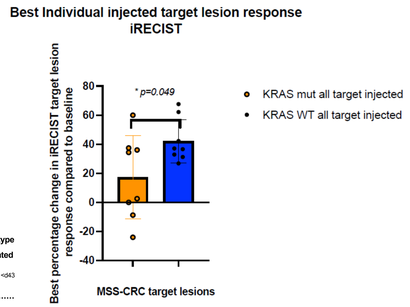
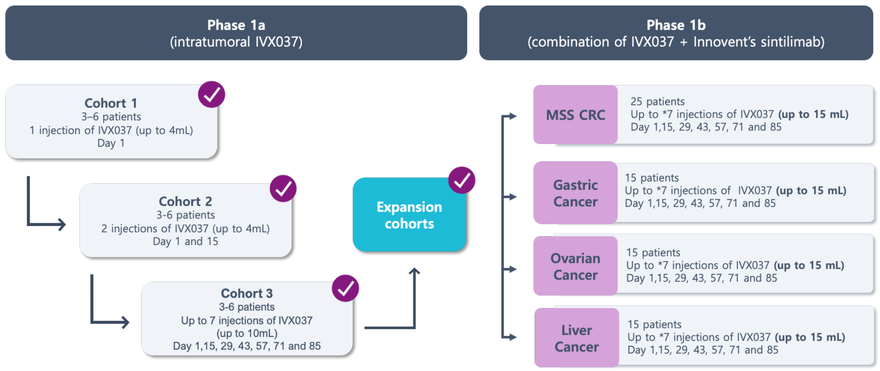


Figure 4. *Best percentage change in Phase 1a iRECIST target injected lesion response compared to baseline. Wt=wild type, KRAS mut = KRAS mutant. Analysis used unpaired student-t test (Preliminary data).*

Figure 3 *Percentage change (iRECIST) of injected target lesions in patients from Phase 1a Cohorts 1, 2 and 3 administered intratumoral IVX037.*

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 had at least one injectable lesion 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. Tumor response was assessed using iRECIST, with the first response assessment occurring at Day 43.

RESULTS

	Total (N = 15)
Age, years	
Median (range)	60 (45 – 74)
Sex, n (%)	
Male	8 (53%)
Female	7 (47%)
Race, n (%)	
Aboriginal or Torres Strait Islander	1 (6%)
Asian	4 (27%)
White	10 (67%)
ECOG Performance Status, n (%)	
0	11 (73%)
1	4 (27%)
Primary Tumor Location, n (%)	
Colon	10 (67%)
Rectum	4 (27%)
Other	1 (6%)
Molecular Status, n (%)	
KRAS mutant	6 (40%)
BRAF mutant	3 (20%)
Wild-type	6 (40%)
MSI Status, n (%)	
MSS	15 (100%)
MSI-H	0 (0%)
Sites of Metastases, n (%)	
Liver	13 (87%)
Lung	7 (47%)
Peritoneum	4 (27%)
Other	10 (67%)
Prior Lines of Therapy	
Median (range)	3 (1 – 3)
Prior Immunotherapy, n (%)	0 (0%)

Table 1*. Patient demographics in Phase 1b (preliminary data)*

Individual Target lesion Response	Evaluable lesions (n=40)	KRAS-BRAF-mut (n=27)	KRAS-BRAF wt (n=13)
CR	0.0%	0.0%	0.0%
PR	2.5%	3.7%	0.0%
SD	42.5%	55.6%	15.4%
DCR	45.0%	59.3%	15.4%

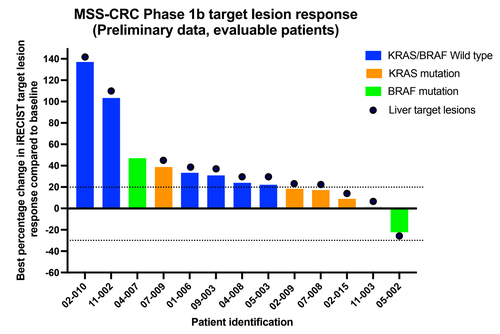


Figure 5*. Best percentage change (iRECIST) of overall target lesion response in patients from the Phase 1b MSS-CRC Cohort. Patients had tumors harboring KRAS or BRAF mutations (MAPK pathway) or were KRAS/BRAF wild-type (WT), as determined by molecular analysis.*

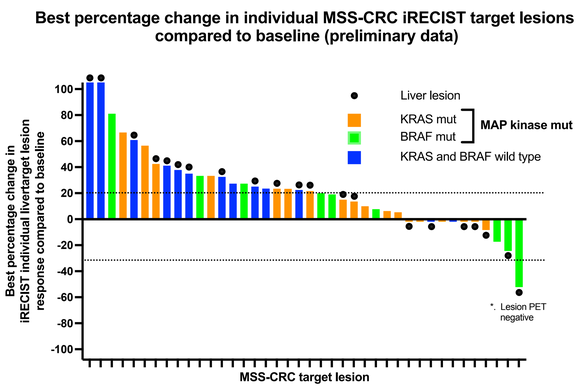


Figure 6. *Best percentage change (iRECIST) of individual target lesions in patients from the Phase 1b MSS-CRC Cohort. Patients had tumors harboring KRAS or BRAF mutations (MAPK pathway) or were KRAS/BRAF wild-type (WT), as determined by molecular analysis.*

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

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

RESULTS cont.

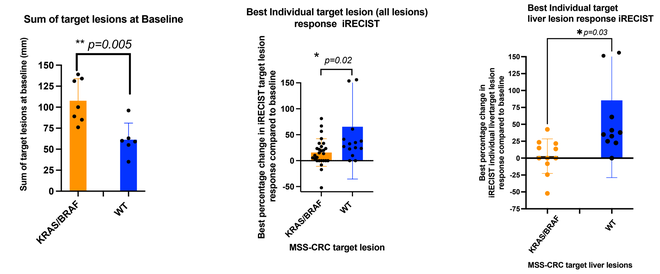


Figure 7. *Phase 1b MSS-CRC Target lesion efficacy update: Individual Response in MAP Kinase Mutated Lesions compared to wild type (Preliminary data).*

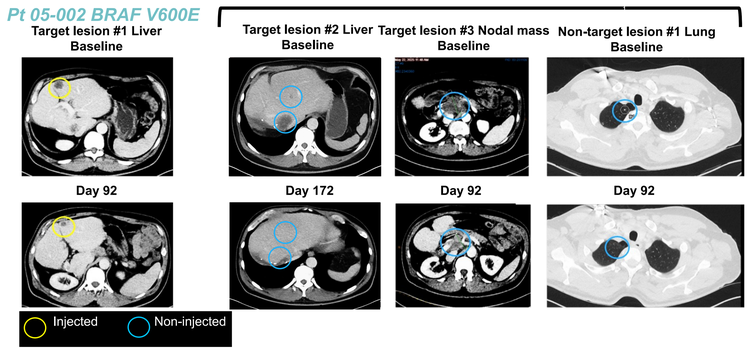
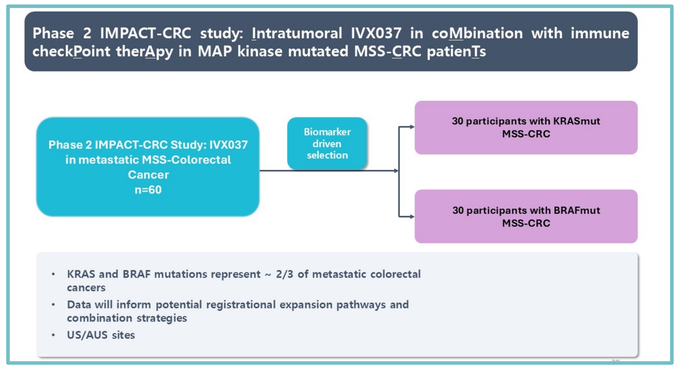


Figure 8. *Phase 1b IVX037 mediates injected and abscopal visceral lesion activity in a BRAF V600E MSS-CRC patient (Preliminary data).*

CONCLUSIONS

- ***Intratumoral IVX037 demonstrates encouraging biological and clinical activity in microsatellite-stable colorectal cancer (MSS-CRC), both as monotherapy and in combination with sintilimab, with enhanced effects observed in KRAS- and BRAF-mutant tumors. This activity may be associated with increased CD55 expression, attenuation of the type I interferon anti-viral response, and enhanced viral replication driven by MAPK pathway activation.***
- ***Nearly all evaluable patients exhibited advanced visceral disease, with 92.3% (12/13) receiving liver lesion directed injections. Baseline target lesion disease was significantly higher in KRAS/BRAF mutated patients compared to that of Wild type patients.***
- ***Disease stabilization was observed across multiple lesions, including hepatic metastases, with notable activity in KRAS/BRAF-mutant tumors.***
- ***Evidence of abscopal activity was identified in a subset of patients, including regression of non-injected liver, lung, nodal metastases, accompanied by reductions in serum CEA and CA19.9 levels.***
- ***The combination of IVX037 and sintilimab was generally well tolerated, with no Grade ≥3 treatment-related adverse events reported for IVX037.***
- ***These preliminary findings support continued clinical development of IVX037 in combination with anti–PD-1 therapy in MSS-CRC, including evaluation in a KRAS/BRAF-mutant–enriched expansion cohort in the proposed Phase 2 IMPACT-CRC study.***

FUTURE DIRECTIONS



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