Proof of concept clinical study by EUS-guided intratumor injection of VCN-01, an oncolytic adenovirus expressing hyaluronidase in patients with pancreatic cancer

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INTRODUCTION

Dense stroma is a hallmark of hard-to-treat cancers such as pancreatic adenocarcinoma. VCN-01 oncolytic adenovirus (Rodriguez-Garcia, et al. Clin Cancer Res. 2015;21(6):1406-18) is designed to replicate in cancer cells with dysfunctional RB1 pathway, improve tumor targeting and express hyaluronidase to enhance virus intratumor spreading and facilitate drug extravasation into the tumor.

OBJECTIVE

Validate the mechanism of action of VCN-01 at preclinical and clinical level, focused on the treatment of advanced pancreatic cancer patients

METHODS

The mechanisms of action of VCN-01 were tested in pancreatic xenograft models after both intravenous and intratumor administration. In a proof of concept Phase I clinical trial study NCT03799744 (8 patients), VCN-01 was escalated up to 1E+11vp per Endoscopic Ultrasound (EUS)-guided intratumor injection (3x) combined with the standard of care, SoC (gemcitabine or nab-paclitaxel/ gemcitabine) in patients with advanced pancreatic adenocarcinoma

RESULTS

VCN-01 alone showed antitumor efficacy in preclinical models and further increased its efficacy when combined with SoC chemotherapy gemcitabine (G) or gemcitabine & nab-paclitaxel (GA). VCN-01 replicated within injected tumors regardless of chemotherapy. Hyaluronidase expression by VCN-01 facilitated tumor extravasation and increased uptake of chemotherapy agents and antibodies.

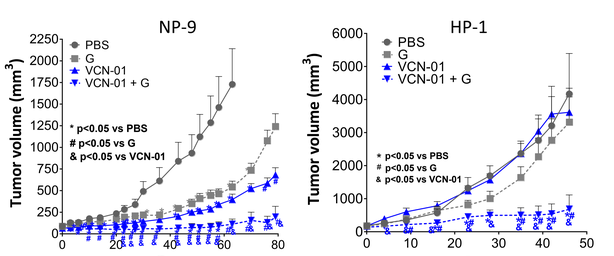

Fig. 1. VCN-01 sensitizes tumors to chemotherapy giving enhanced antitumor activity in animal models.

RESULTS CONTINUED

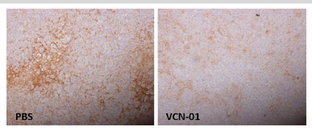

Fig.2. VCN-01 is able to reduce hyaluronan content within human tumors grown in mice.

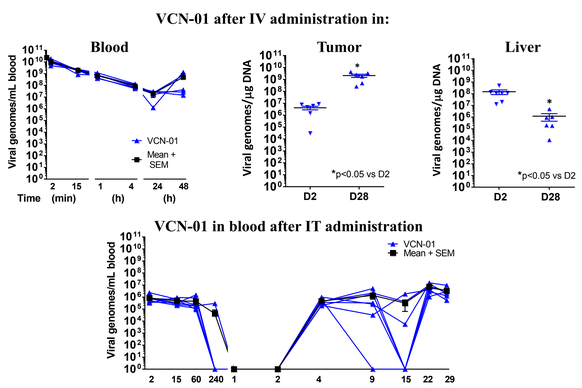

Fig. 3. VCN-01 pharmacokinetics evidences secondary viral replication peaks in mouse blood after IV and IT administration. VCN-01 replicates within tumors over time.

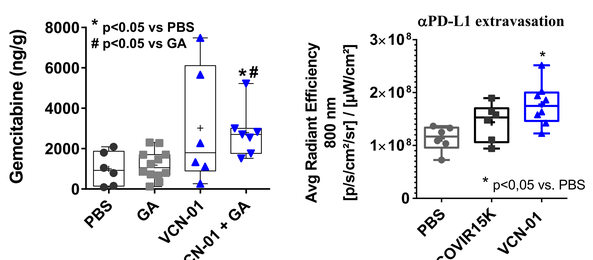

Fig. 4. VCN-01 enhances the extravasation of chemotherapy and therapeutic antibodies into tumors grown in mice.

RESULTS CONTINUED

Data obtained from a Phase 1 clinical trial of VCN-01 administered by repeated intratumor injection showed that the combination treatment was generally well-tolerated although 3 events of dose limiting toxicity (DLTs) were found at highest dose (2 of them by transaminase increase and 1 of them by Localized Intraabdominal Collection).

When combined with chemotherapy, VCN-01 stabilized the injected lesion in all patients although no impact on survival was observed compared to reference data for gemcitabine / nab-paclitaxel. Of note, a patient showed long progression free survival of 134 weeks. VCN-01 was detected as secondary peaks in blood several days after injection and in tumors at day 20-28, indicating virus replication. Hyaluronidase PH20 presence in sera was confirmed for all patients injected at 1E+11vp. Elastography of VCN-01-treated tumors evidenced reduction in tumor stiffness regardless of nab-paclitaxel coadministration.

Table 1

Adverse Reaction *(Preferred term)*	N° patients treated	All grades (N=39) N° patients observed	%	Grade ≥3 (N=7; 18%) N° patients observed	%
Fatigue/Asthenia	8	6	75,0%	1	12,5%
Pyrexia	8	4	50,0%	0	0,0%
Hypertransaminemia	8	3	37,5%	2	25,0%
Neutropenia	8	3	37,5%	1	12,5%
Thrombocytopenia	8	2	25,0%	0	0,0%
Anorexia	8	2	25,0%	0	0,0%
Arthomialgia	8	2	25,0%	0	0,0%
Neurotoxicity	8	2	25,0%	0	0,0%
Constipation	8	2	25,0%	0	0,0%
Localised intraabdominal fluid collection	8	1	12,5%	1	12,5%
Febrile Neutropenia	8	1	12,5%	1	12,5%
Hypophosphatemia	8	1	12,5%	1	12,5%
Anemia	8	1	12,5%	0	0,0%
Leucopenia	8	1	12,5%	0	0,0%
GGT increased	8	1	12,5%	0	0,0%
Diarrhea	8	1	12,5%	0	0,0%
Dyspepsia	8	1	12,5%	0	0,0%
Nausea	8	1	12,5%	0	0,0%
Vomiting	8	1	12,5%	0	0,0%
Epistaxis	8	1	12,5%	0	0,0%

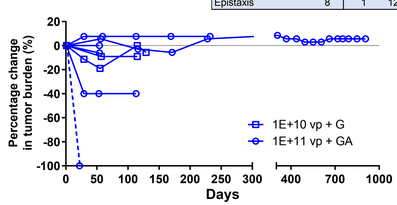

Fig. 5. Antitumor activity of intratumor injections of VCN-01 in patients shows that the injected lesion remained stable or decreased in size.

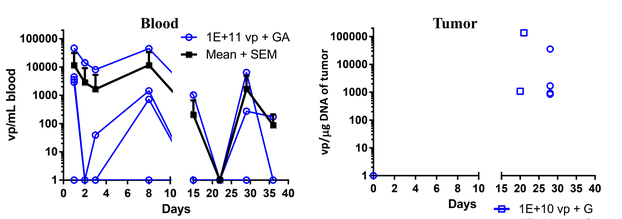

Fig 6. VCN-01 is detected in patient's blood over the time showing secondary viral replication peaks and in tumors after 20-28 days post treatment, suggesting viral replication.

RESULTS CONTINUED

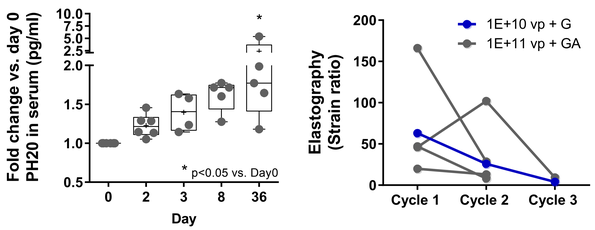

Fig. 7. Hyaluronidase PH20 expression in serum increases over time suggesting production of PH20 by VCN-01 replication and stroma disruption effects are observed in patients' tumor.

CONCLUSIONS

- The preclinical and clinical results presented here confirm VCN-01 oncolytic capacity in preclinical models and patients with PDAC.
- VCN-01 replicates and expresses hyaluronidase after intratumor injection both in preclinical models and in patients with pancreatic cancer.
- Enhanced chemotherapy access and reduction of tumor stiffness favors local control of pancreatic tumors treated with VCN-01 + standard of care.
- These results support further evaluation of the efficacy of VCN-01 combined with chemotherapy for the treatment of advanced PDAC.
- Given VCN-01 mechanism of action, the combination of VCN-01 plus other treatments in cancers that have high HA content is also supported.

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MBP, AMB, MVM, EB, CB and MC are employees and RA is consultant in VCN Biosciences. MC and RA are co-inventors of one patent application concerning the expression of hyaluronidase by oncolytic adenoviruses and both have ownership interest in VCN Biosciences.

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