VCN-01 changes tumor stroma when administered systemically in combination with Durvalumab (MEDI4736) in subjects with recurrent/ metastatic squamous cell carcinoma of the head and neck (R/M HNSCC): Biological data of a Phase I Study

Abstract 0136

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Forward Looking Statements

This presentation includes forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995. In some cases forward-looking statements can be identified by terminology such as "may," "should," "potential," "continue," "expects," "anticipates," "intends," "plans," "believes," "estimates," and similar expressions, and include statements regarding the potential of VCN-01 and its ability to overcome key oncolytic virus challenges, oncolytic viruses being promising cancer therapeutics, near term clinical advancement of VCN-01 including initiation of a Phase 2 PDAC clinical trial in Q4 2022, the proposed PDAC Phase 2 clinical trial design and the potential of the albumin shield to enhance the OV systemic delivery and the potential of the other Theriva Biologics' product candidates. These forward-looking statements are based on management's expectations and assumptions as of the date of this press release and are subject to a number of risks and uncertainties, many of which are difficult to predict that could cause actual results to differ materially from current expectations and assumptions from those set forth or implied by any forward-looking statements. Important factors that could cause actual results to differ materially from current expectations include, among others, Theriva Biologics' product candidates demonstrating safety and effectiveness, as well as results that are consistent with prior results, the ability to initiate a Phase 2 PDAC clinical trial in Q4 2022; the ability to complete clinical trials on time and achieve the desired results and benefits, continuing clinical trial enrollment as expected; the ability to obtain regulatory approval for commercialization of product candidates or to comply with ongoing regulatory requirements, regulatory limitations relating to Theriva Biologics' ability to promote or commercialize their product candidates for the specific indications, acceptance of product candidates in the marketplace and the successful development, marketing or sale of VCN's and Theriva Biologics' products, developments by competitors that render such products obsolete or non-competitive, Theriva Biologics' ability to maintain license agreements, the continued maintenance and growth of Theriva Biologics' patent estate, the ability to continue to remain well financed, and other factors described in Theriva Biologics' Annual Report on Form 10-K for the year ended December 31, 2021 and its other filings with the SEC, including subsequent periodic reports on Forms 10-Q and 8-K. The information in this presentation is provided only as of the date of this release, and Theriva Biologics undertakes no obligation to update any forward-looking statements contained in this release on account of new information, future events, or otherwise, except as required by law.

Trial Design & Methods

- STUDY POPULATION:
  - Recurrent/Metastatic (R/M) HNSCC patients who have progressed during or after treatment with immune-checkpoint inhibitors. Eligibility Criteria include the selection of patients with levels of neutralizing antibodies against adenovirus ≤1/350 dilution at the moment of inclusion in the study
- DESIGN:
  - Phase I dose-escalation study testing two dose levels of i.v. VCN-01 (3,3E12 & 1E13 viral particles, [vp]) combined with a fixed dose of Durvalumab (1500 mg) using 3+3 design
- TREATMENT SCHEDULES:
  - Concomitant (single dose VCN-01 and Durvalumab on day 1, CS)
  - Sequential (single dose of VCN-01 on day -14 and Durvalumab on day 1; SS), both followed by Durvalumab q4 weeks until progression or intolerable toxicity. Fresh tumor biopsies were taken at baseline, post-VCN-01 and post-Durvalumab

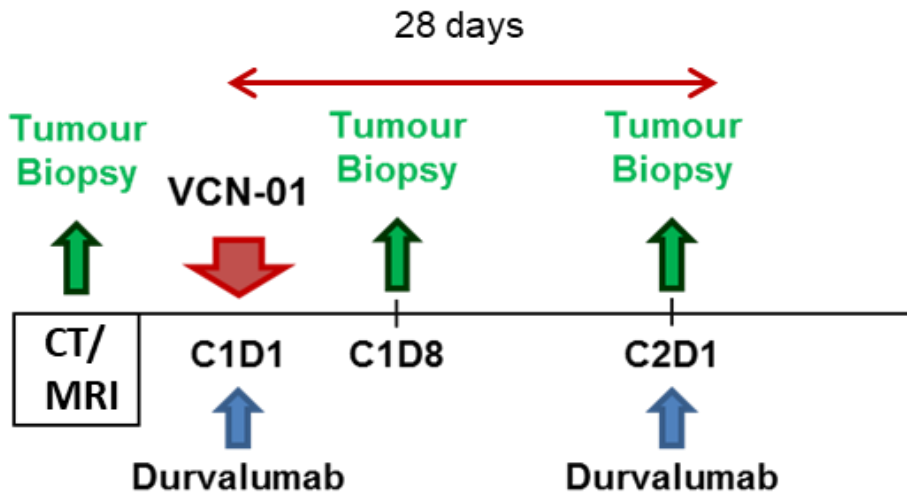
ARM I

VCN-01 in combination with Durvalumab

C-1
single dose
3,3E12 vp/patient

C-2
single dose
1E13 vp/patient

3+3 Dose escalating Design



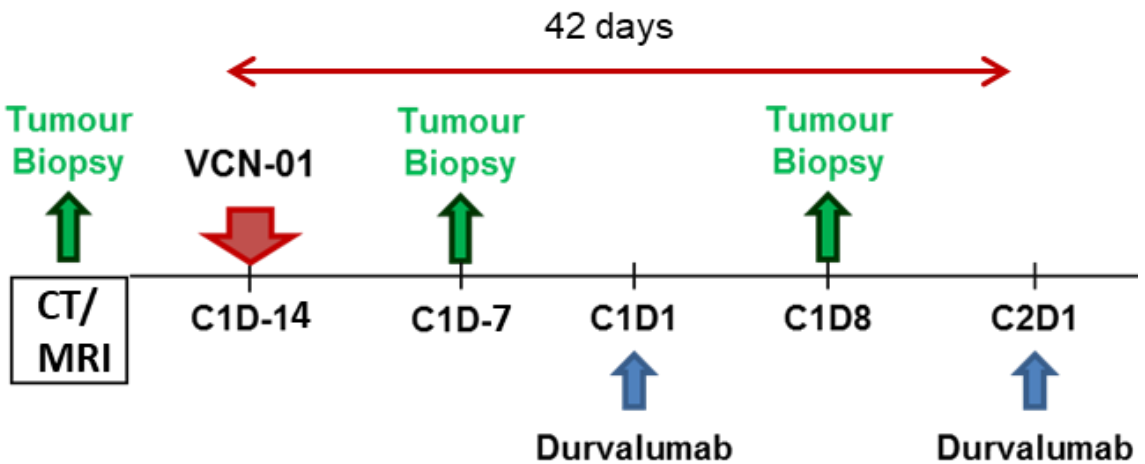
ARM II

VCN-01 in combination with Durvalumab in a sequential schedule

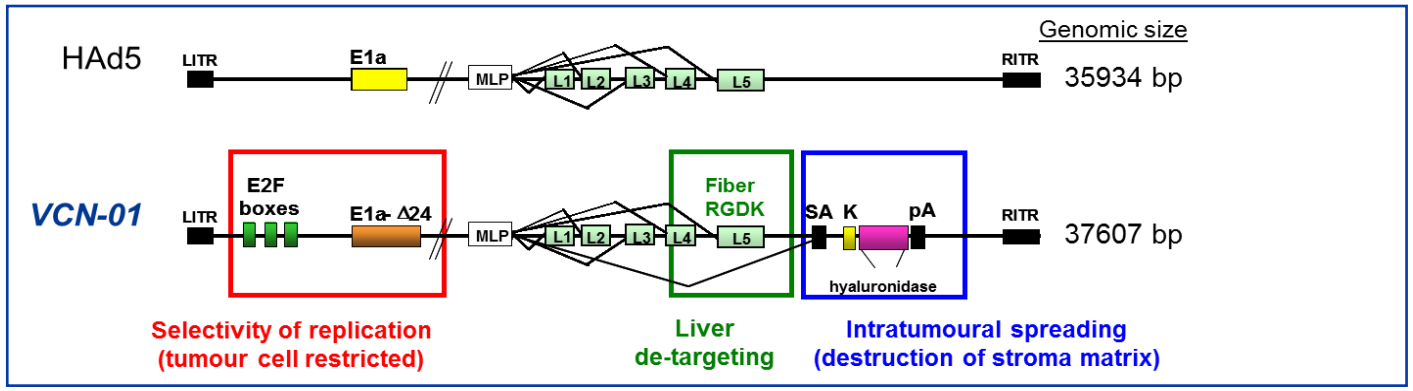
S-1
single dose
3,3E12 vp/patient

S-2
single dose
1E13 vp/patient

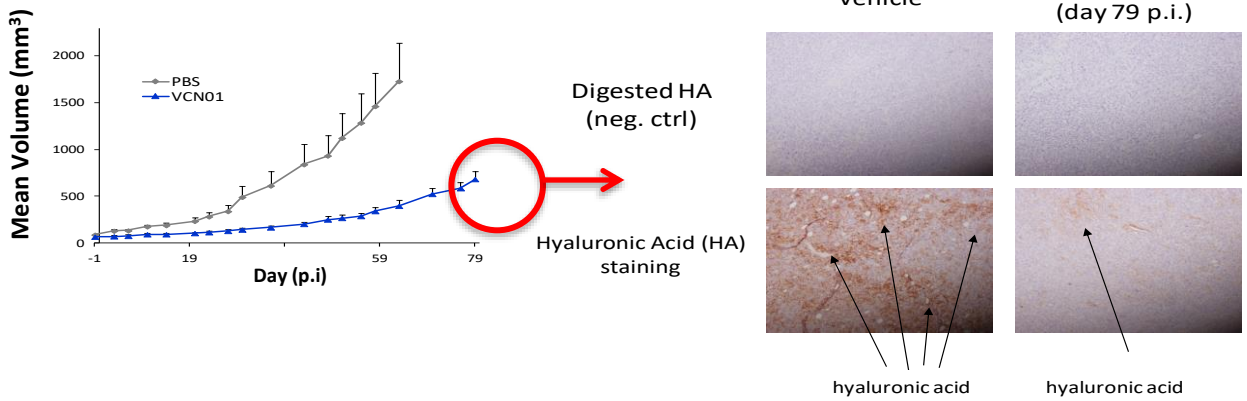
3+3 Dose escalating Design



VCN-01 is an Ad5 OV expressing hyaluronidase

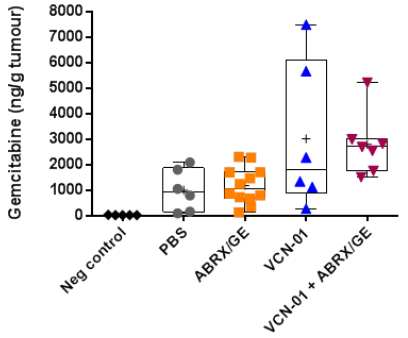


VCN-01 Antitumour Activity in NP-9 (pancreatic) s.c. mouse model

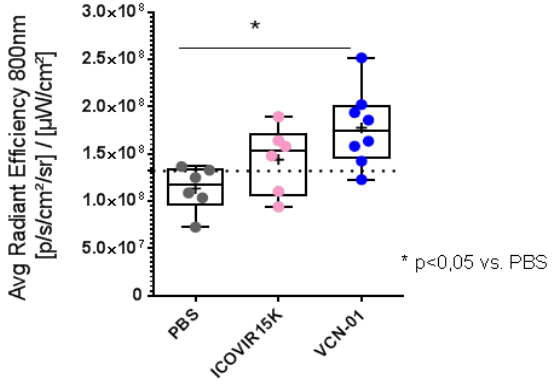


VCN-01-mediated enhanced extravasation of Cx & therapeutic antibodies

Gemcitabine



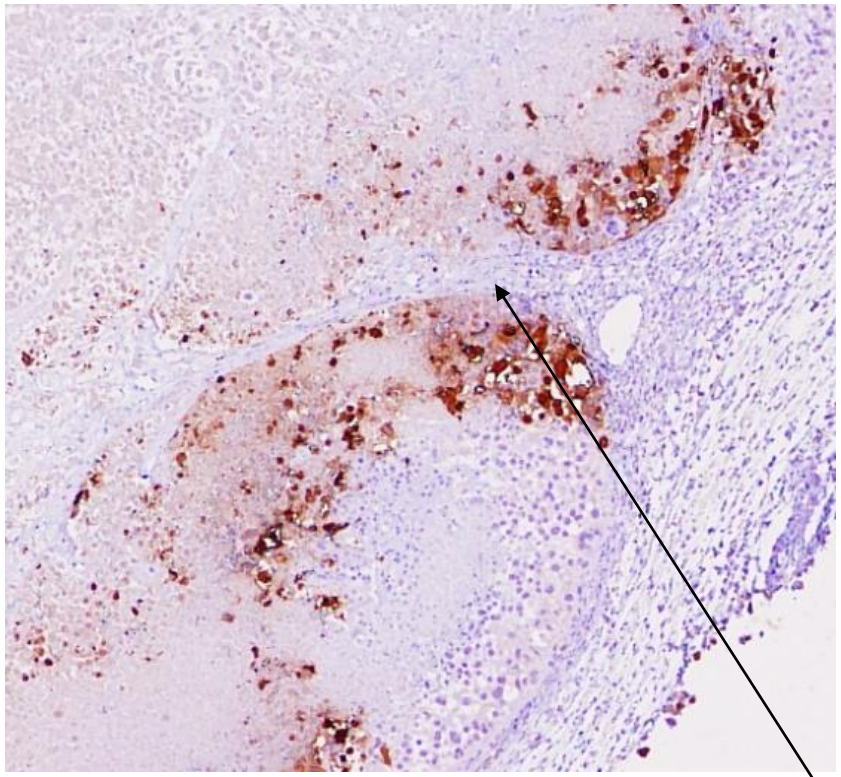
Antibody

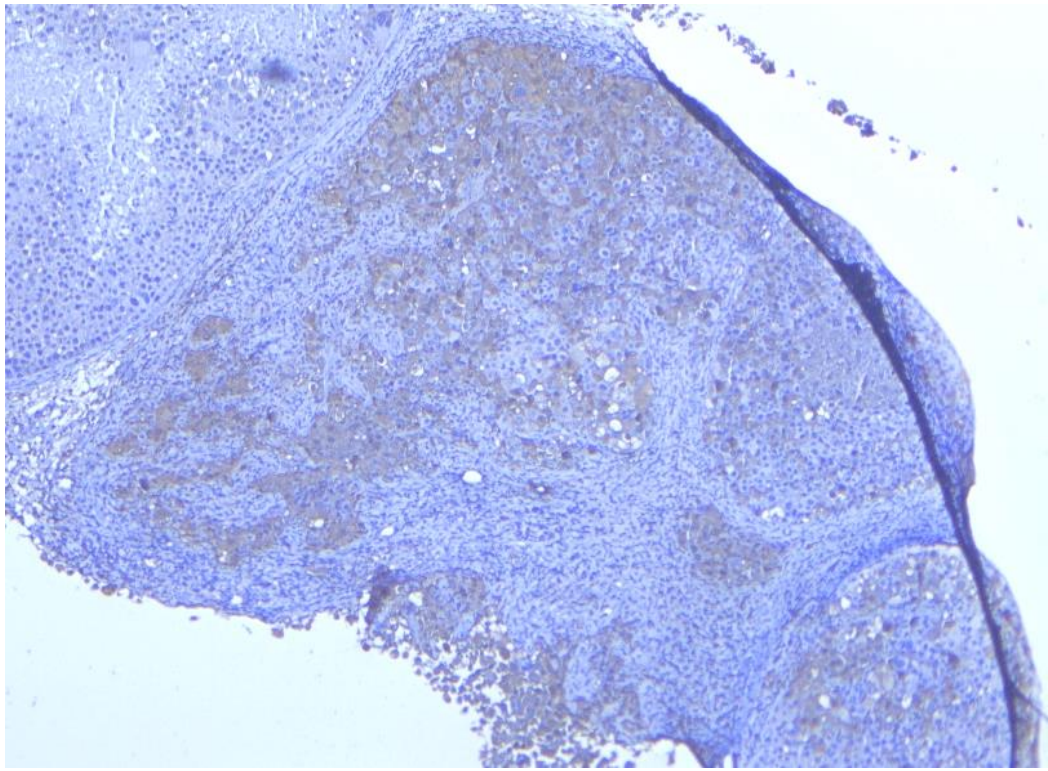


Hyaluronic acid (PBS)

Hyaluronic acid (VCN01)

The stromal barrier to virus spread





Extracellular matrix (Hyal+) + Cancer Associated Fibroblasts (CAFs FAP+)

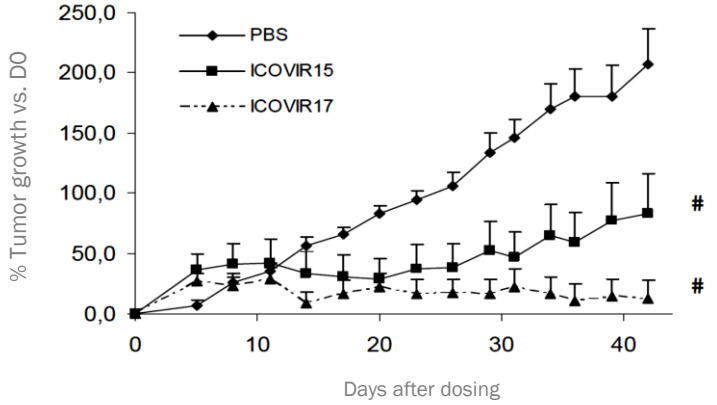
Pre-clinical: Hyaluronidase expression favors antitumor activity of IV administration

ICOVIR15: without Hyal
ICOVIR17: with Hyal (as VCN-01)

Athymic nude mice
sc tumors

IT administration

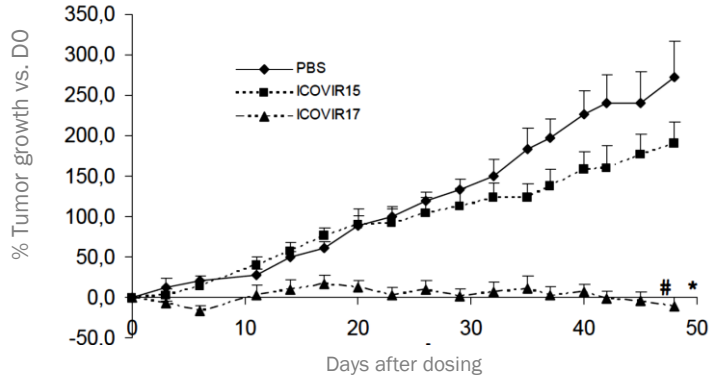
(2E+9 vp /tumor)



SkMel-2

IV administration

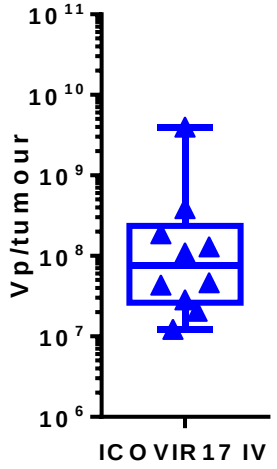
(5E+10 vp /tumor)



Guedan et al. 2010

Intratumor content after IV

(48 h.p.i.)



1% INPUT DOSE

Lower tumor load after IV dosing is capable of inducing enhanced antitumor activity

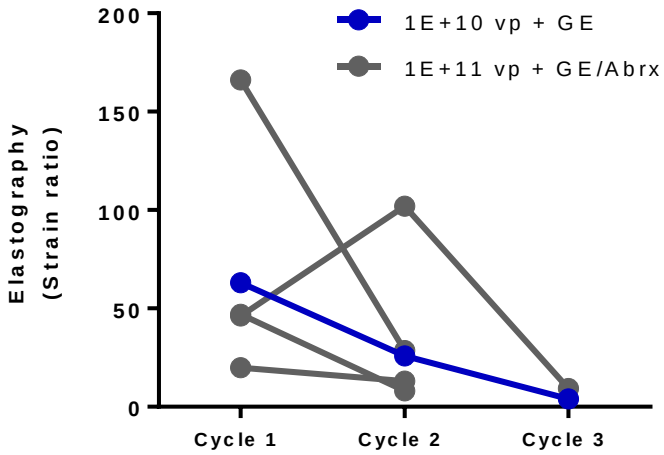
Clinical: Hyal expression by VCN-01 is functional in PDAC patients

P-VCNA-002 trial

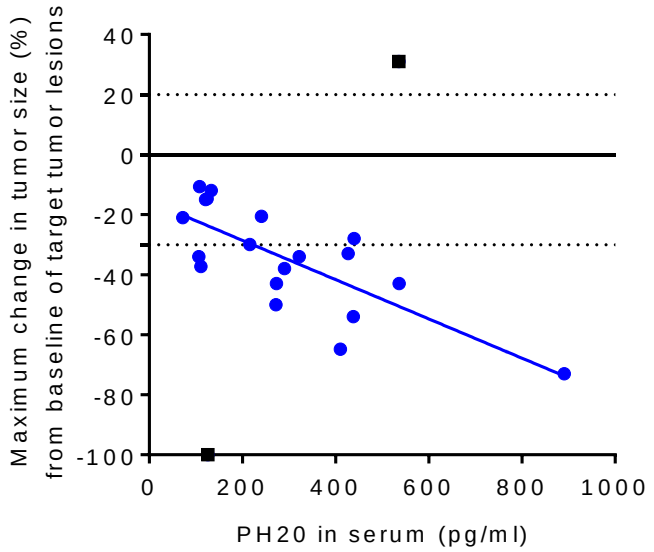
P-VCNA-001 trial

VCN-01-induced Hyal expression reduces pancreatic tumor stiffness

Tumor Elastogram in pancreatic tumors



Serum levels of Hyal correlates with tumor burden reduction

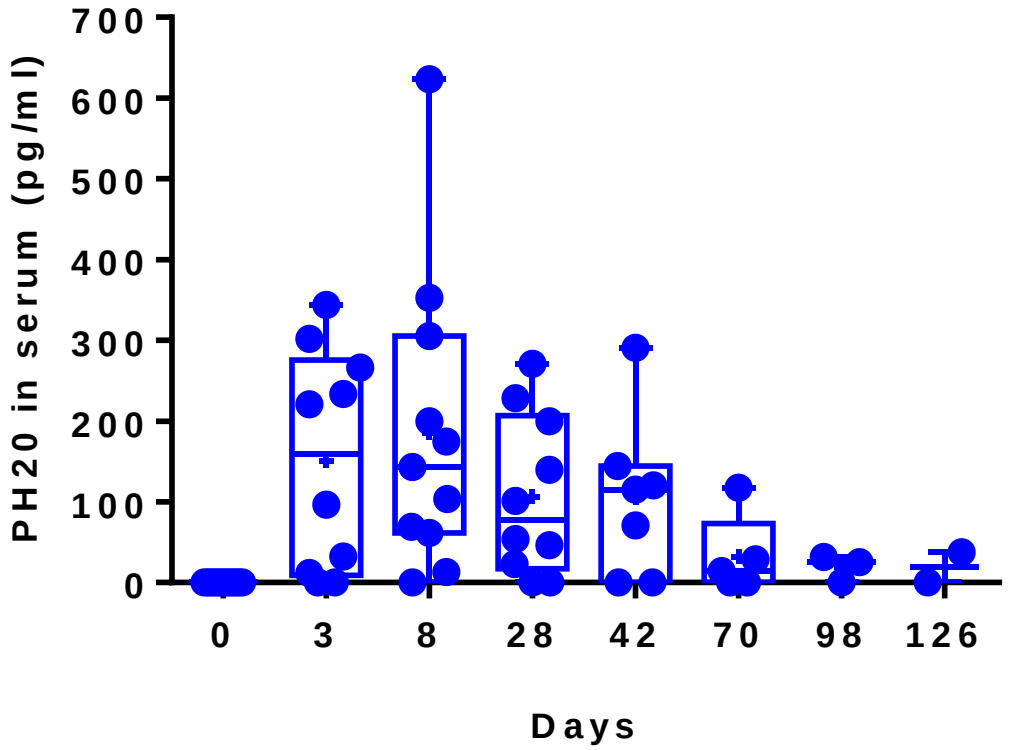


Spearman correlation:
p=0.005, r=-0.61, 95% CI -0.84 to -0.21.

R/M HNSCC Clinical: Quantification of PH20 Expression in Serum

PH20 enzyme in serum from treated patients was measured by ELISA at different time points.

Durable expression is depended on continued virus replication

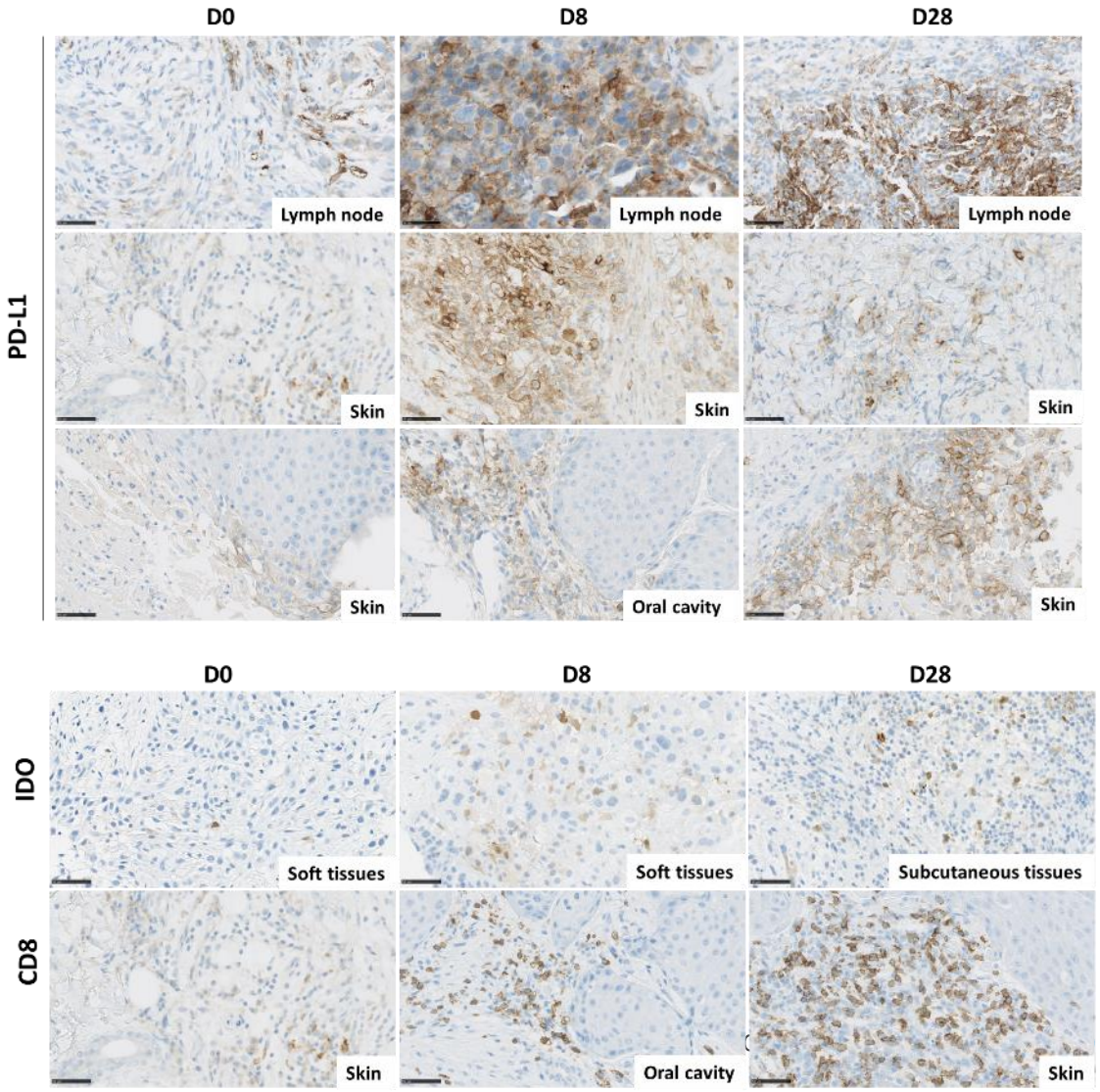


R/M HNSCC Trial : Analysis of MoA in Clinical Samples

	CD8 /Treg axis	PD-1 / PD-L1 axis	IFNg/ IDO pathway	CTLA4 pathway
D8	55% ↓Tregs* (6/11)	55% ↑PD-1 (6/11)	64% ↑IDO (7/11)	36% ↑CTLA-4 (4/11)
	64% ↑CD8 (7/11)	73% ↑PD-L1 (8/11)		
D28	63% ↓Tregs* (5/8)	56% ↑PD-1 (5/9)	60% ↑IDO (6/10)	33% ↑CTLA-4 (3/9)
	50% ↑CD8 (5/10)	80% ↑PD-L1 (8/10)		

Summary of immune markers variations by IHC of all paired biopsies (Sequential & Concomitant Arm samples). % of samples showing modulation (positive / total analyzed samples)
*Including FoxP3 & CD25 staining

IV administered VCN-01 can induce durable up-regulation of PD-L1 in tumor cells



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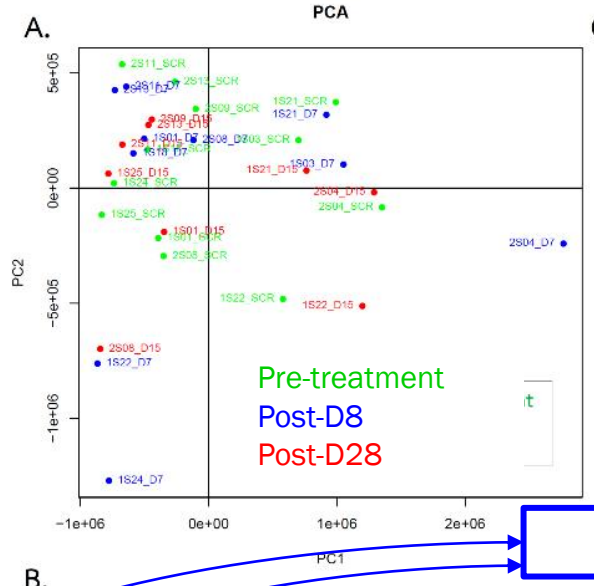
R/M HNSCC Trial: Analysis of MoA in Clinical Samples

VCN-01 induces Transcriptomic Changes in Tumor Microenvironment

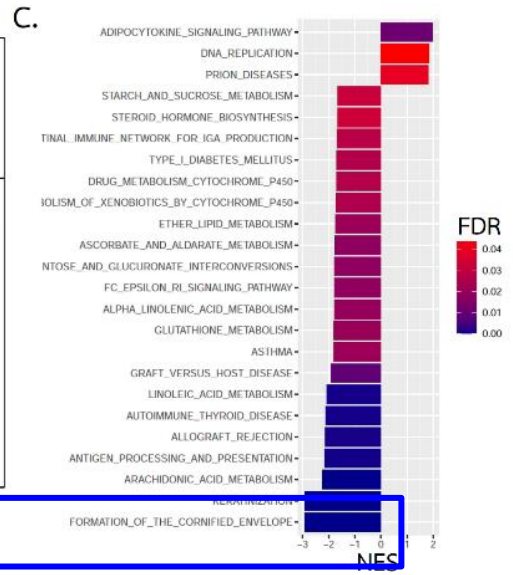
Principal Component Analysis[1]

including all the Pre- and Post-treatment samples

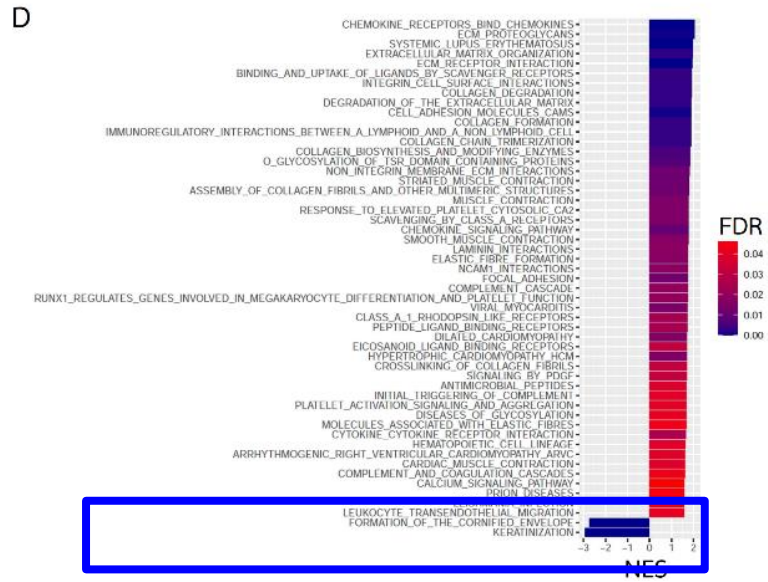


Most significant Reactome and KEGG pathways in GSEA (Gene Set Enrichment Analysis) [1]

analysis D8 vs Pre-treat.



analysis D28 vs Pre-treat.



B.

Gene	Gene product	log2FoldChange	padj	
CIDEC	Cell Death Inducing DFFA Like Effector C	5.524	0.047	Up D7
TAGLN3	Transgelin 3	1.615	0.037	
GPR3	G Protein-Coupled Receptor 3	1.157	0.039	
ABP1	Auxin-binding protein 1	-1.636	0.013	Down D7
CD207	CD207 Molecule	-1.960	0.044	
MEGF10	Multiple EGF Like Domains 10	-2.008	0.043	
OSTalpha	Organic solute transporter alpha	-2.179	0.039	
CD1E	CD1E Molecule	-2.316	0.010	
ATP10B	ATPase Phospholipid Transporting 10B	-2.556	0.044	
FCER1A	Fc Epsilon Receptor Ia	-2.687	0.006	
LOC285629	.....	-2.818	0.001	
LCE1B	Late Cornified Envelope 1B	-7.921	0.006	

Sustained differential gene expression profiles associated with downregulation of matrix-related pathways

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R/M HNSCC Trial : Analysis of MoA in Clinical Samples

Perfusion changes induced by VCN-01

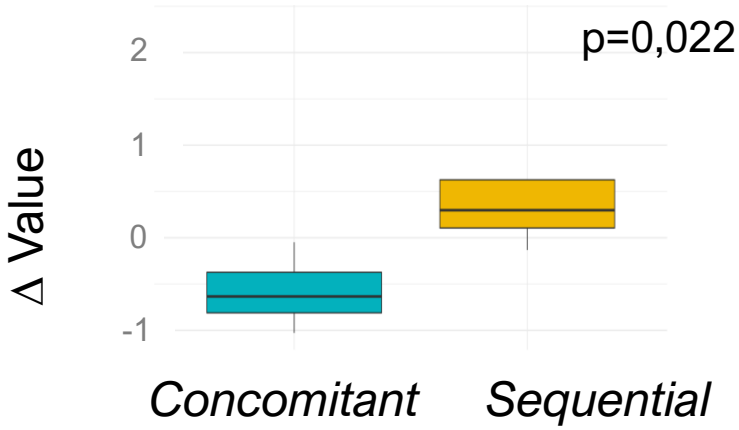
Dynamic contrast enhanced (DCE) were acquired from MRI images in Trial NCT03799744 (Systemic VCN-01 in HNSCC & Durvalumab[1]

Imaging biomarkers were obtained by a non-invasive imaging post-processing procedure. The delta (D) radiomic features for the lesions treated sequentially were extracted between the screening and the 1st follow-up (corresponding to week 8)

Radiomic markers suggest VCN-01 increases perfusion from the extravascular space to the intravascular space

K_{ep} marker

(rate transfer constant extravascular space ←→ blood)



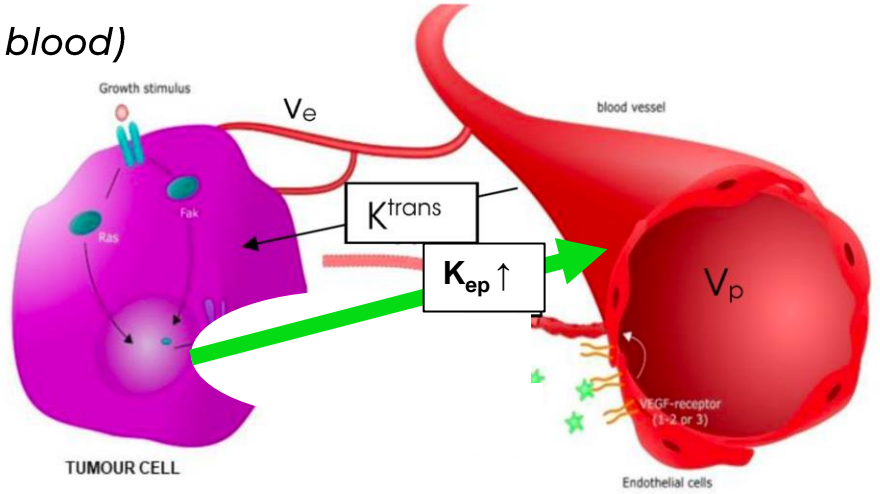
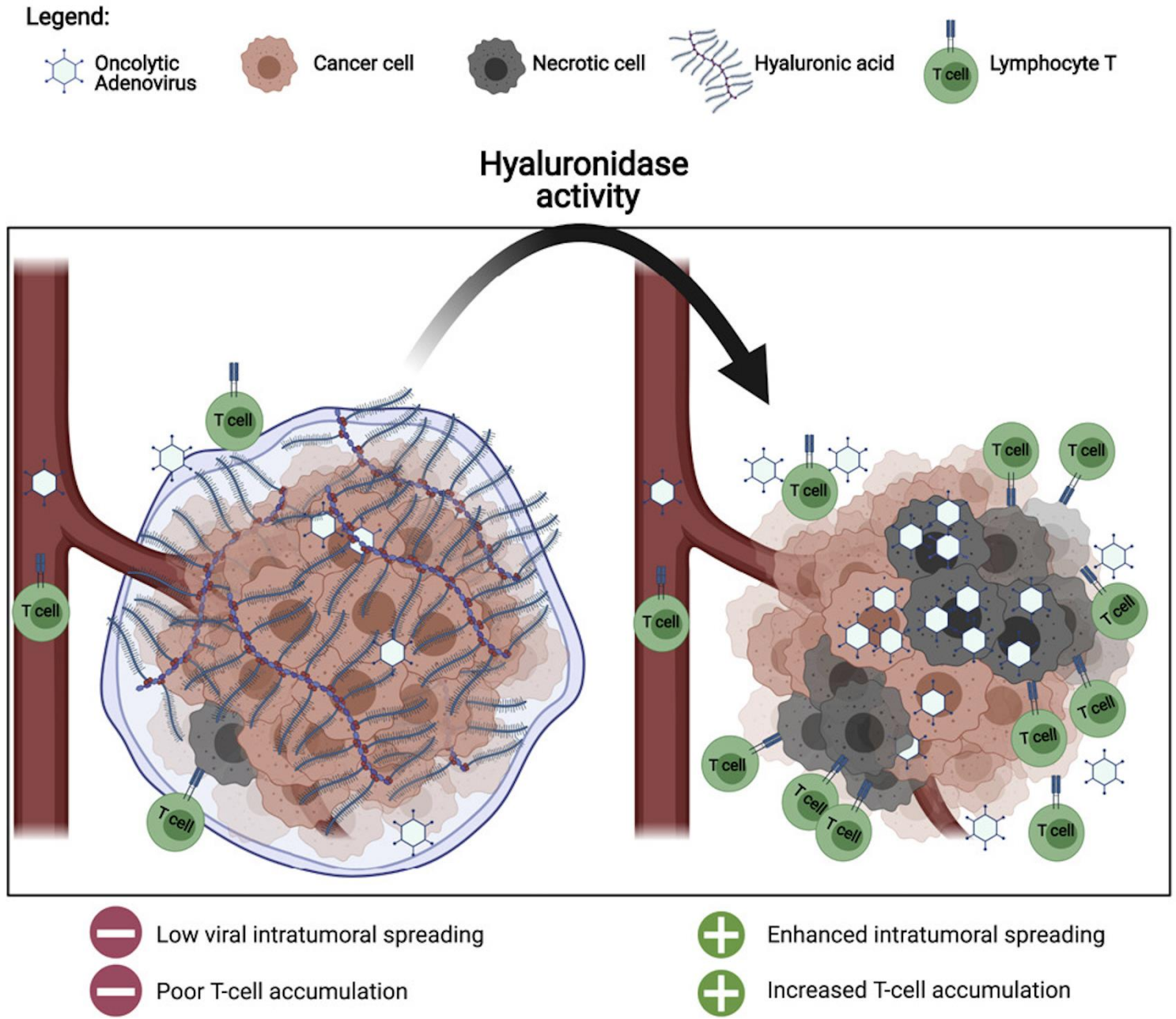


Figure 1. Pharmacokinetic perfusion model

VCN viruses vs. Halozyme PEG-PH20

	PEG-PH20	VCN-01
Distribution	Sera levels: 2500 pg/ml *(Infante et al. 2018)* High systemic exposure	Sera levels: sustained levels between D1-D28 (400 -1000 pg/ml) IT production linked to virus replication
Debulking effect	Controversial impact of Hyal on tumor growth *(Stern et al. 2005)*	Strong cell killing effect (IC_{50}: ranging 0,1-10 vp/cell)
Immune system interactions	Hyal favors ICIs uptake *(Clift et al., 2019)*	Virus replication inducing inflammation & generation of neoantigens, whereas Hyal favors CD8 infiltration & ICIs uptake



M. Farrera-Sal et. Al. Mol Ther Oncolytics. 2021 Sep 24; 22: 27–35

Clinical Efficacy by RECIST PDAC Trial

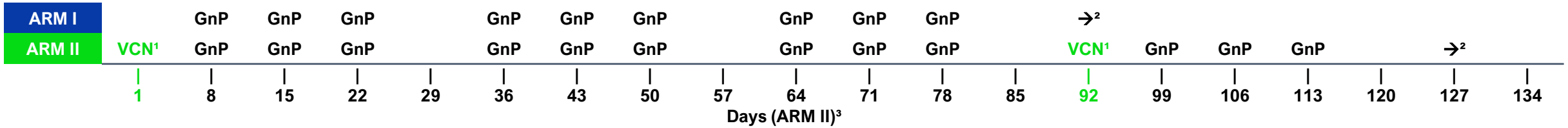
IT dosing (P-VCNA-002) & IV dosing (P-VCNA-001 trials)

Identical target population: Pancreatic adenocarcinoma patients treated with GE/Abrx

	SoC (GE/Abrx)	**VCN-01 IT** (x3 injections)	**VCN-01 IV**
		N=7	**N=22 (pooled data Part II & III)**
CR (Complete Response)	*<1%*	0 (0%)	1 (4,5%)
PR (Partial Response)	*23%*	0 (0%)	10 (46%)
SD (Stable Disease)	*27%*	6 (85%)	10 (46%)
Long Survival (>1 year)	*<1%*	1 (14%)	8 (36%)
ORR (Overall Response Rate)	*23%*	0 (0%)	11 (50%)
PFS (median)	*5,5 months*	3,6 months (2,8-25,5)	7,22 months (1,6-19,9)
OS (median)	*8,5 months*	8,2 months (3,0-25,5)	13,35 months (2,6-48,4)

Upcoming VCN-01 Phase 2 Controlled Clinical Trial in PDAC: VIRAGE Trial

- Enrollment
  - Open-label, randomized Phase 2b study conducted at up to 25 sites across the US, Spain and Germany
  - Patients ≥18 y.o. with histologically confirmed, first line metastatic pancreatic ductal adenocarcinoma
  - Established clinical standard-of-care (SOC) therapy is gemcitabine/nab-paclitaxel (Abraxane®)
- Treatment Arms (Randomization 1:1, N=92)
  - Arm I: Gemcitabine/nab-paclitaxel standard of care (GnP 28-day cycles)
  - Arm II: GnP with VCN-01 (IV; days 1 and 92) administered 7-days before first dose of GnP in the cycle



[1]VCN-01 1x10[13] vp by IV infusion (50 mL solution in NaCl 0.9%). [2]Continue GnP cycles until disease progression, intolerable/unacceptable toxicity, consent withdrawal or investigator's decision. [3]Dosing days for ARM II shown for clarity of comparison between arms; ARM I cycle 1 will also start on Day 1 and will not be delayed 7 days.

THANK YOU!!

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