Corporate Overview

December 2022

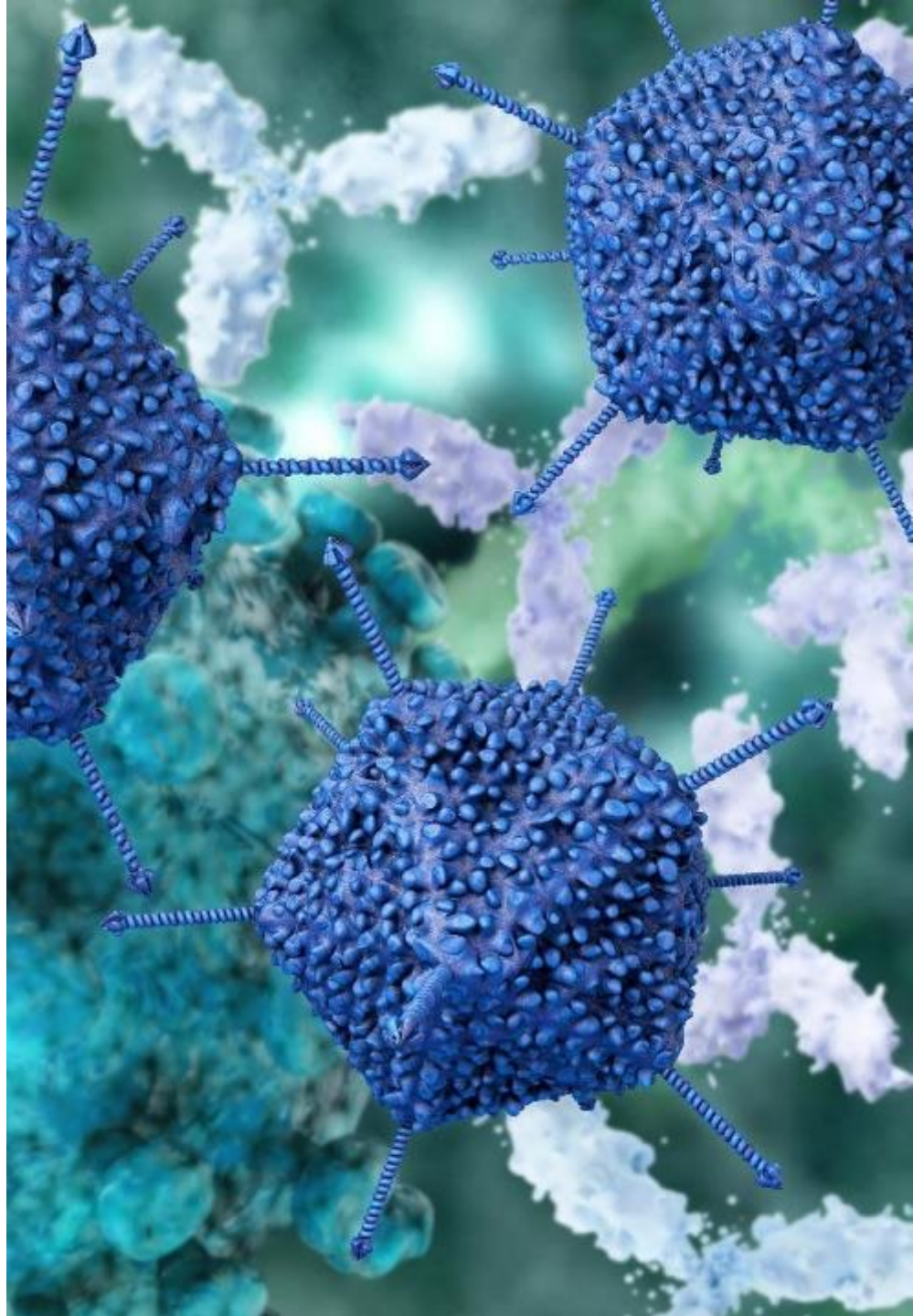
Theriva BIOLOGICS

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 and an Rb Company sponsored clinical trial late 2023, 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 and an Rb Company sponsored clinical trial late 2023; 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.

Overview

- Theriva Biologics (NYSE American: TOVX) is developing unique oncolytic viruses (OVs) optimized for systemic administration and selective tumor destruction
- Lead clinical product VCN-01 is entering a Phase 2 clinical trial in metastatic pancreatic ductal adenocarcinoma
- Phase 1 clinical trials support evaluation of VCN-01 in additional indications (retinoblastoma) and combinations (CAR-T cells, CPIs)
- Proprietary Albumin Shield™ platform and leading OV discovery engine enable development of a distinct pipeline of products for a wide array of cancers
- Programs supported by strong current cash position with runway to 2024[1]



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[1]Approximately $50.5M at 30Sep2022

Seasoned Leadership Team

Steven Shallcross

Chief Executive Officer, Chief Financial Officer

Served as the Company's CEO since 2018 and CFO since joining the Company in 2015

Deep operational, financial and international biotech industry experience and proven track record of leading the financial development and strategy in the public sector

Senseonics · VANDA PHARMACEUTICALS INC. · Innocoll · nuo THERAPEUTICS

Manel Cascalló PhD

General Director, EU Subsidiary

Expertise in oncolytic adenovirus clinical development, received several patents for the use of adenovirus as antitumoral agents and authored many peer-reviewed scientific publications

Deep regulatory experience and serves as an independent expert for the European Medicines Agencies (EMA)

VCN BIOSCIENCES

Frank Tufaro PhD

Chief Operating Officer

Extensive executive experience, as well as clinical and academic experience in the development of oncolytic viruses based on herpes simplex and adenovirus, with numerous patents and peer-reviewed scientific publications

VCN BIOSCIENCES · MediGene · DNAtrix THERAPEUTICS

Vince Wacher PhD

Head Corporate Development

Nearly 30 years leading corporate strategy, partnering, research, clinical development, and intellectual property programs for start-ups, small companies, and new business units within large companies

Development experience across oncology, infection, GI, metabolic diseases, transplantation, and drug delivery

EASTMAN · Verva Pharmaceuticals

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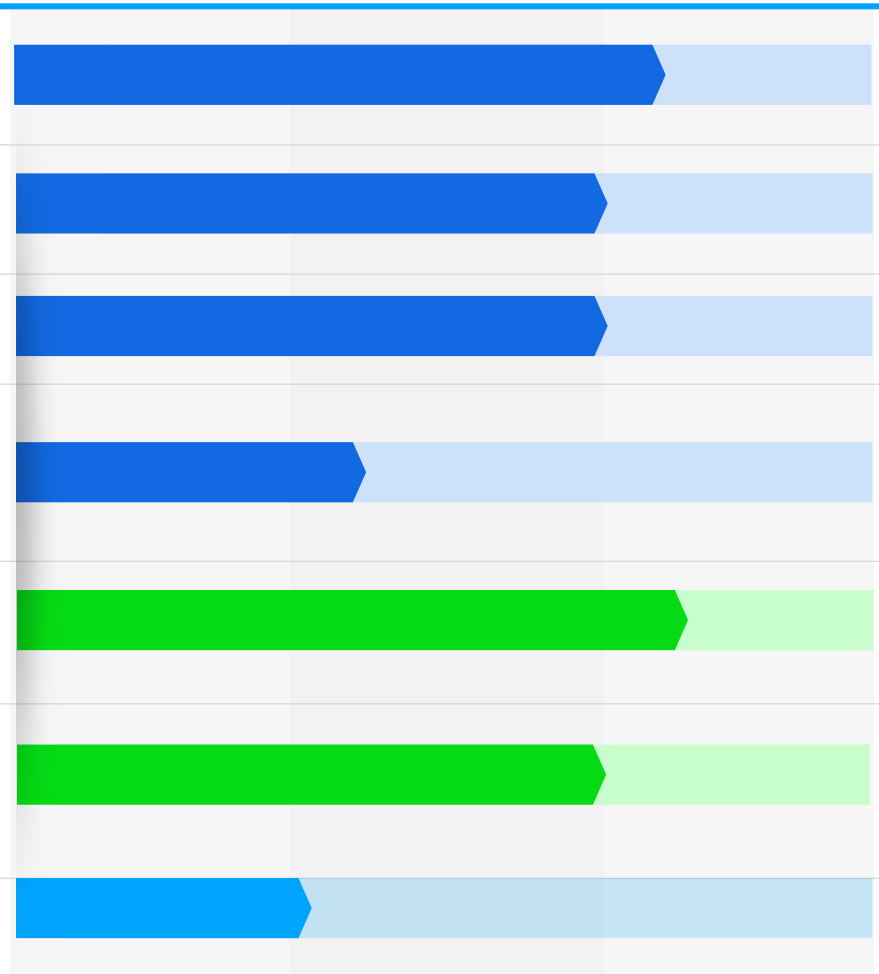
Pipeline

Technology	Candidate	Target	Pre-IND / Phase 1 / Phase 2	Collaborators	Status*
Stroma Degrading Oncolytic Virus (OV)	VCN-01	Pancreatic Cancer (IV) with gemcitabine/nab-paclitaxel			Ph 2 Trial Initiation Expected Q4'22 (ODD EU)
		Retinoblastoma (IVit)			Company Sponsored Clinical Trial Initiation Expected H2'23 (ODD US)
		HNSCC (IV) + durvalumab		ICO Institut Català d'Oncologia	Enrollment Complete Initial Data H2'22
		Solid Tumors – Brain, Ovarian, PDAC (IV)		LEEDS; Penn	Investigator Sponsored Studies U. Penn initiated, U. Leeds screening
Oral β-lactamase	SYN-004	Prevention of aGVHD in allo-HCT		Washington University in St. Louis	Cohort 2 Phase 1b/2a Data Expected Q1'24
Oral IAP	SYN-020	Potential indications include NAFLD/NASH, celiac, radiation enteritis		MGH Massachusetts General Hospital	Reported MAD Topline Data Q2'22
Albumin Shield OVs	VCN-11	Solid tumors (IV)		ICO Institut Català; IDIBELL	Ongoing Preclinical Studies



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*Based on Management's current beliefs and expectations. aGVHD acute graft-vs-host disease; allo-HCT allogeneic hematopoietic cell transplant. IAP recombinant bovine intestinal alkaline phosphatase II.. HNSCC head and neck squamous cell carcinoma. IV intravenous. IVit intravitreal. MAD multiple ascending dose. ODD Orphan Drug Designation.

Oncolytic Viruses are Promising Cancer Therapies

Opportunities

- Can be engineered to infect and directly destroy a wide range of tumor types
- Can be combined with other cancer treatments (chemotherapy, CPI, CAR-T)
- Can induce a persistent anti-tumor response by the patient immune system for additional tumor cell killing

Needs

- Systemic administration to enable infection and destruction of primary and metastatic tumors
- Selective action in tumor cells to avoid off-target effects in healthy tissues and organs e.g. liver
- Stroma protective barrier must be overcome to expose the tumor to the immune system and facilitate access by the OV and cancer therapies

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Reviewed in Balachandran (2019) Gastroenterology 156:2056. Hemminki (2020) J Hematol Oncol 13:84. Khare (2012) J Virol 86:2293. CAR-T chimeric antigen receptor T cell. CPI immune checkpoint inhibitor.

VCN-01 is a Uniquely Engineered Oncolytic Adenovirus

SYSTEMIC

- High doses
- Highly replicating
- Accesses primary and metastatic lesion

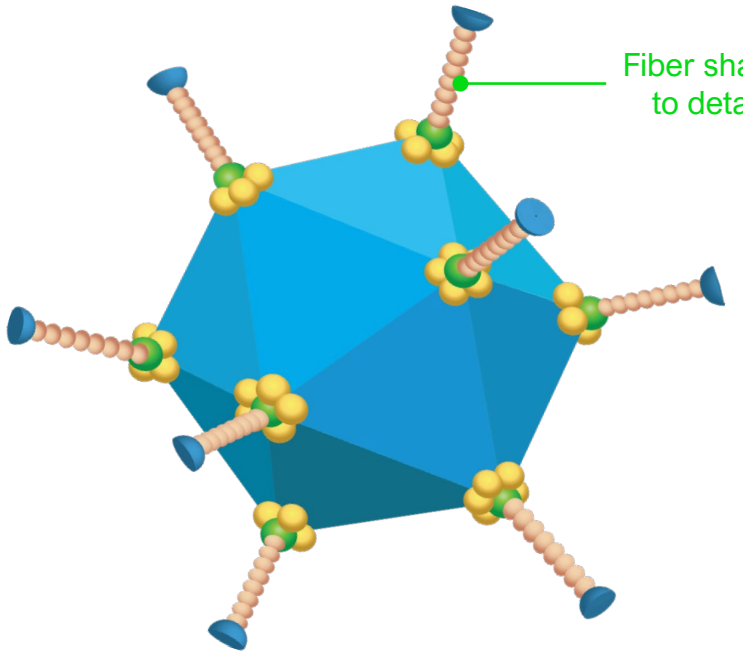
SELECTIVE

- Replicates only in Rb-E2F defective tumors (not healthy cells)[1]
- Designed to reduce liver tropism, improve tumor uptake
- Transgene PH20 expressed only after virus replication[2]

STROMA DEGRADING

- Expresses PH20 (hyaluronidase) to degrade tumor stroma[3]
- Exposes tumor to the immune system
- Designed to increase tumor penetration and dissemination by VCN-01 and concomitant cancer therapies

VCN-01 Genetically Modified Ad5



E2F binding++ → E1a-Δ24 → MLP → PH20

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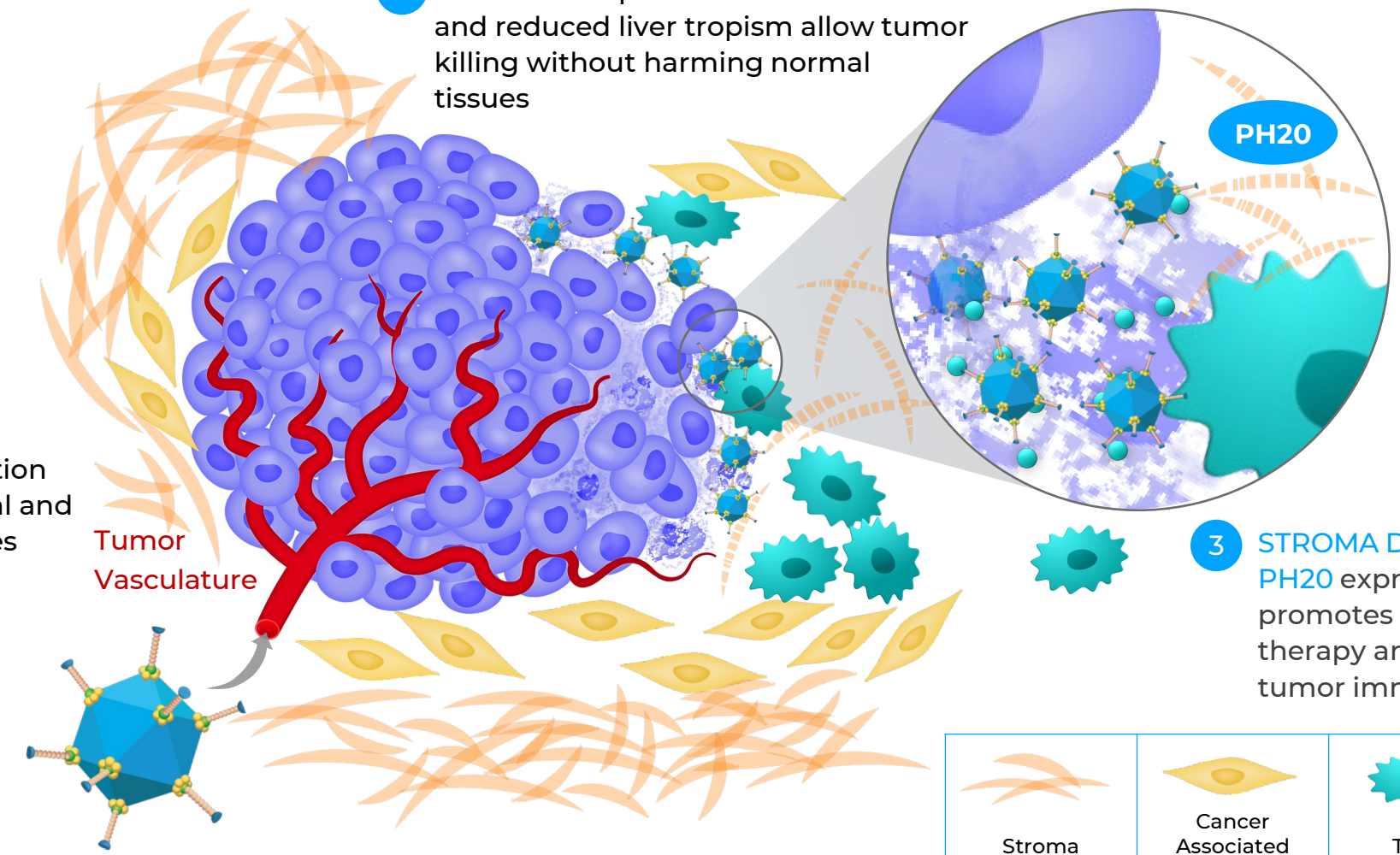
[1]Most if not all solid tumors; Giacinti (2006) Oncogene 25:5220; Polager (2009) Nat Rev Cancer 9:738. [2]Transgene expression under control of virus major late promoter (MLP). [3]PH20 is human testicular hyaluronidase enzyme. For additional details and references see Appendix.

Unique Mechanism of Action for Theriva OV Products

1 SYSTEMIC administration enables access to local and metastatic cancer sites

2 SELECTIVE replication in cancer cells and reduced liver tropism allow tumor killing without harming normal tissues

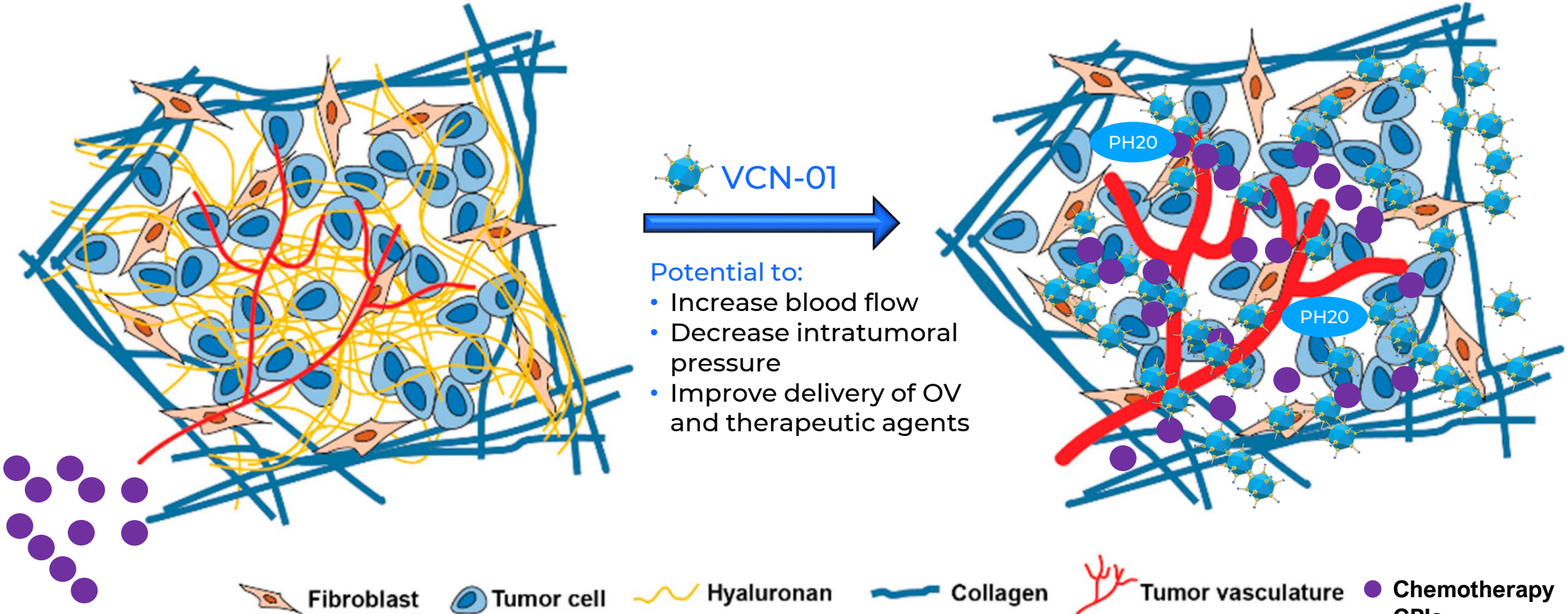
3 STROMA DEGRADING enzyme PH20 expressed after infection promotes more effective therapy and improves anti-tumor immune response



VCN-01 Secretes PH20 in Infected Tumor Cells to Degrade Stroma

Pre-treatment

Post-treatment



Potential to:

- Increase blood flow
- Decrease intratumoral pressure
- Improve delivery of OV and therapeutic agents

[1]Most adapted from Maloney (2019) Cancers 11:772

Extensive VCN-01 Phase 1 Clinical Experience

Collaborating with world-leading institutions, 77 patients treated to date

Location	Phase	Indication	Co-therapy	Route	Status	NCT or Other
Multicenter (ESP)	1	Part I: Solid tumor Part II: PDAC Part III: PDAC	Part I: None Parts II,III: Gemcitabine + nab-Paclitaxel	IV	Complete[1]	NCT02045602
Multicenter (ESP)	1	PDAC	Gemcitabine + nab-Paclitaxel	IT	Complete[2]	NCT02045589
Hospital Sant Joan de Déu, Barcelona	1	Retinoblastoma	None	IVit	Partial data available	NCT03284268
Institut Català d'Oncologia (ICO)	1	HNSCC	Durvalumab	IV	Enrollment complete; initial data H2'22	NCT03799744
U. Leeds	1	Adult brain tumors	None	IV	Screening	ISRCTN 517624869
U. Pennsylvania	1	PDAC, Ovarian	huCART-meso[3]	IV	Ongoing	NCT05057715

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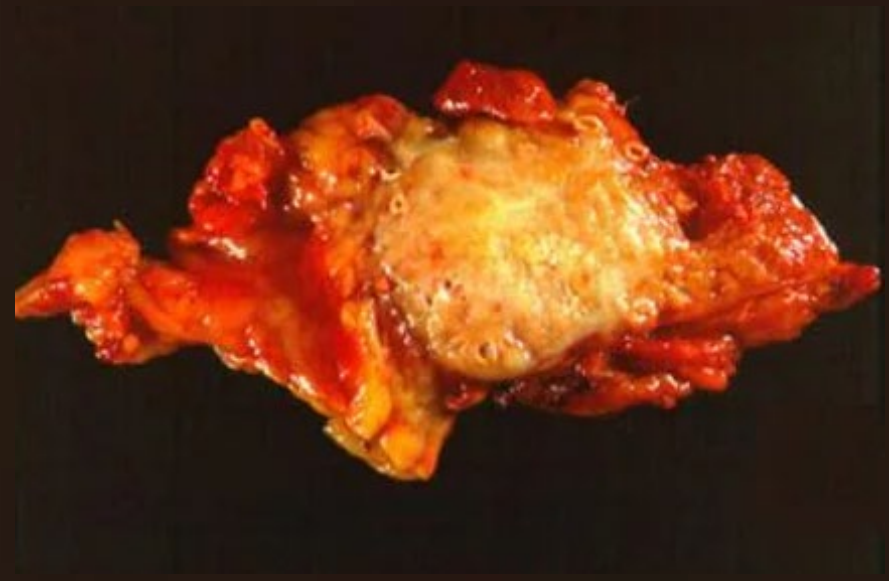
[1]Garcia-Carbonero (2022) J Immunother Cancer 10:e003255. [2]Bazan-Peregrino (2021) J Immunother Cancer 9:e003254. [3]huCART-meso are autologous T cells engineered to express an extracellular single chain variable fragment (scFv) with mesothelin specificity. HNSCC head and neck squamous cell carcinoma. IV intravenous. IT intratumoral. IVit intravitreal.

VCN-01 Clinical Program in PDAC

Pancreatic Ductal Adenocarcinoma

- Pancreatic adenocarcinoma (PDAC) is a deadly cancer with the highest mortality of all solid tumors
  - Accounts for the 3rd highest no. cancer deaths in the US each year (4th in EU)[1,2]
  - Median survival 9-11 months from diagnosis; 1 year survival 24%
- PDAC has a dense stroma that acts as a barrier to therapy
  - Stromal hyaluronan is associated with low immune response and poor prognosis[3,4]
- Treatment options for metastatic PDAC are limited
  - First-line chemotherapies include gemcitabine + nab-paclitaxel and (m)FOLFIRINOX
  - Checkpoint inhibitors have been largely ineffective



Pancreatic adenocarcinoma resected from the pancreas body and tail

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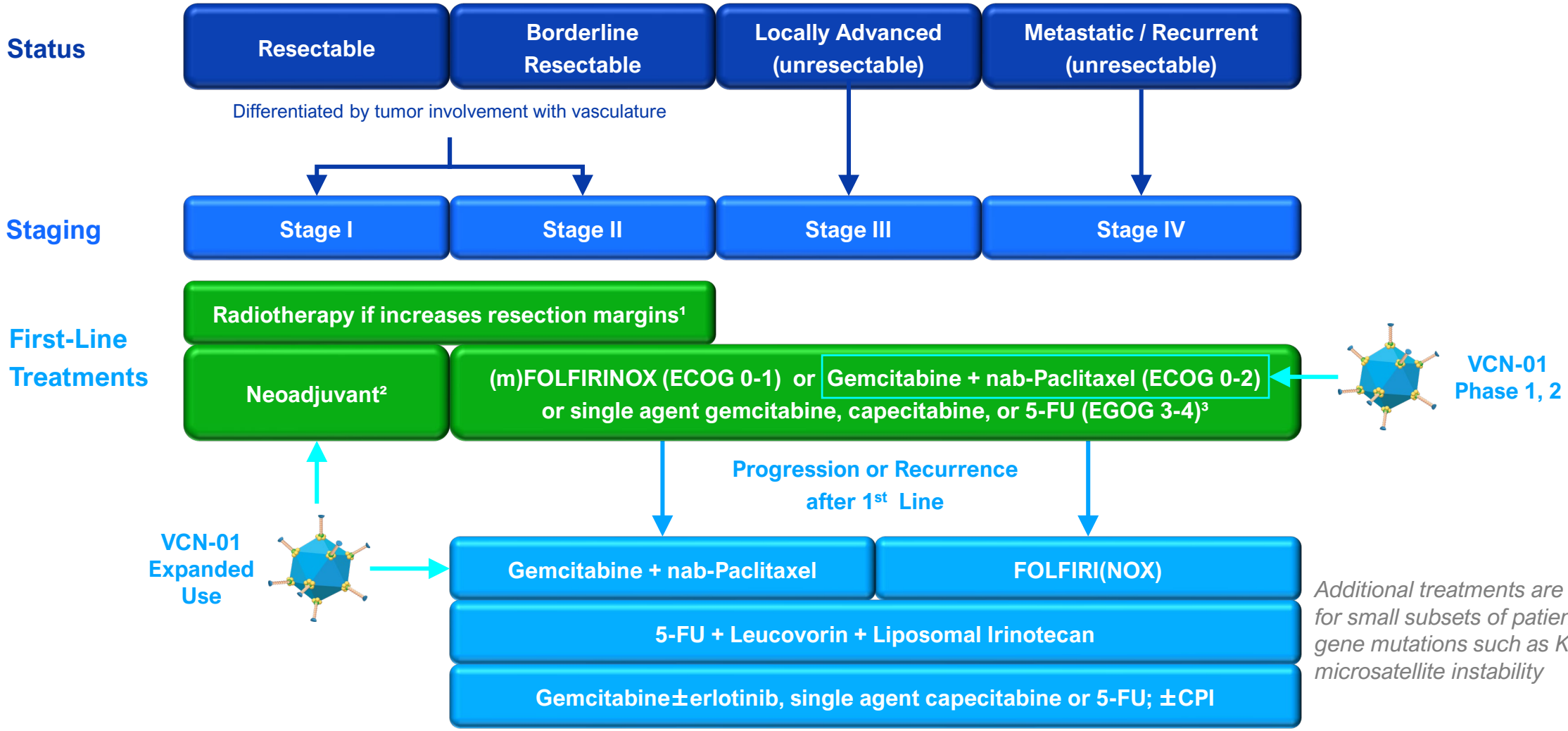
[1]Bengtsson (2020) Sci Rep 10:16425. [2]Carioli (2021) Ann Oncol 32:478.. [3]Tahkola (2021) Sci Rep 11:12216. [4]Placencio-Hickok (2022) Pancreatology 22:92. For additional details and references see Appendix. (m)FOLFIRINOX (modified) leucovorin + 5-FU + irinotecan + oxaliplatin. nab-Paclitaxel nanoparticle paclitaxel albumin-bound

Multiple Opportunities for VCN-01 in Pancreatic Cancer

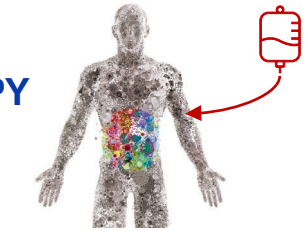


Additional treatments are available for small subsets of patients with gene mutations such as KRAS, microsatellite instability

[1]Used in <20% of PDAC cases. [2]Neoadjuvant chemotherapy is identical to first-line. [3]ECOG Eastern Cooperative Oncology Group Performance Status 0-1. [4]CPI checkpoint inhibitor (e.g., pembrolizumab). (m)FOLFIRINOX (modified) leucovorin+5-FU+irinotecan+oxaliplatin. nab-Paclitaxel nanoparticle albumin-bound paclitaxel. Adapted from Tempero (2021) *J Natl Compr Canc Netw* **19:**439.

VCN-01 Phase 1 Clinical Trial Established IV Dosing Regimen

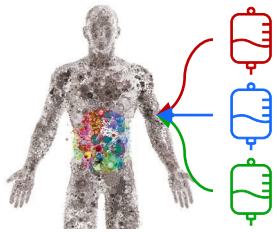
ARM I
MONOTHERAPY
Solid tumors (16)



VCN-01 Dose Finding[1]

- ✓ Multicenter, open-label, dose escalation study [NCT02045602]
- ✓ Single IV doses of VCN-01 alone or with standard-of-care (**SoC**) chemotherapy gemcitabine/nab-paclitaxel (Abraxane®)
- ✓ Evaluate safety and tolerability, recommended Phase 2 dose

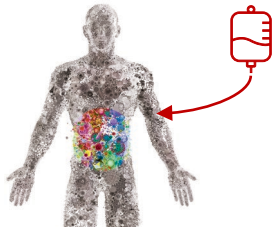
ARM II
CONCOMITANT
PDAC (12)



VCN-01[2]
nab-Paclitaxel[3]
Gemcitabine[4]

SoC chemotherapy 28-day cycles starting Day 29

ARM III
SEQUENTIAL
PDAC (14)



VCN-01[5]
nab-Paclitaxel
Gemcitabine[4]

SoC chemotherapy 28-day cycles starting Day 36

Cycle 1 Day 1 | 8 | 15 | 22 | 29 | 36

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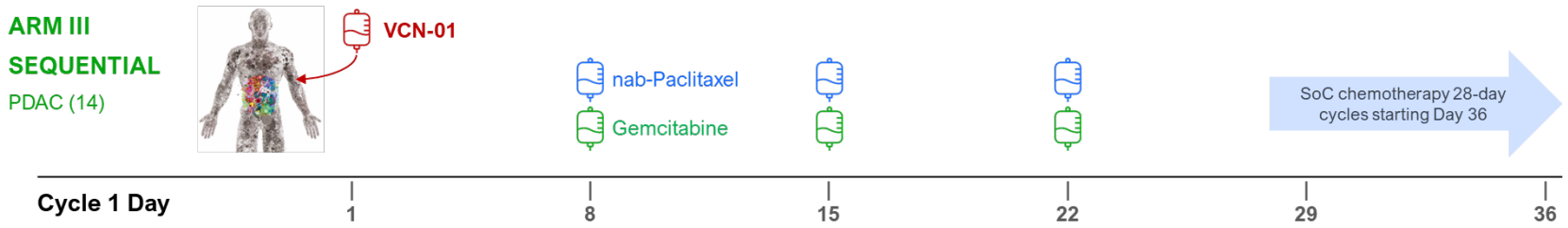
[1]Single dose of VCN-01 ($1x10^{11}$ to $1x10^{13}$ vp/dose) administered by 10 min IV infusion. [2]VCN-01 doses $3.3x10^{12}$ vp (n=6) and $1x10^{13}$ vp (6). [3]nab-Paclitaxel (Abraxane®; 30 min infusion) administered at least 4 hours after VCN-01. [4]Gemcitabine (30 min infusion) administered immediately after Abraxane® infusion. [5]VCN-01 doses $3.3x10^{12}$ vp (8) $1x10^{13}$ vp (6). Garcia-Carbonero (2022) J Immunother Cancer 10:e003255.

Positive VCN-01 Phase 1 Data Encourage PDAC Phase 2 Trial

Favorable Survival with SEQUENTIAL VCN-01 + SoC Compared to Published SoC alone				
Treatment Group (n)[1]	**Response n (%)**	**Median Survival (OS) Months**	**Long Duration Survival >12 months**	**>27 months**
VCN-01 3.3x10[12] vp/patient (6)	1 (16.7%)	13.1		
VCN-01 1.0x10[13] vp/patient (6)	5 (83.3%)	20.8		
VCN-01 both doses (12)	**6 (50.0%)**	**13.5**	**8 (75%)**	**3 (25%)**
Published SoC Alone[2]	**23%**	**8.5**		



[1]Garcia-Carbonero (2022) J Immunother Cancer 10:e003255 [NCT02045602]. [2]Von Hoff (2013) NEJM 369:1691. [3]Only 12 of 14 evaluable for response and survival endpoints. **SoC** gemcitabine/ nab-paclitaxel (Abraxane®) administered IV on days 1, 8 and 15 of each chemotherapy cycle with cycles repeated every 28-days. vp virus particles.

Most Common IV VCN-01 Related AEs (Multicenter, Spain)[1]

ADVERSE EVENTS	Part I (Alone, n=16)		Part II (Concomitant, 12)[2]		Part III (Sequential, 14)[3]	
	Grade 1-2	Grade ≥3	Grade 1-2	Grade ≥3*	Grade 1-2	Grade ≥3
Febrile neutropenia	-	-	-	2 (16.7%)	-	-
Neutropenia/Neutrophil count decreased	2 (12.5%)	-	1 (8.3%)	1 (8.3%)	-	-
Thrombocytopenia/Platelet count decreased	1 (6.3%)	1 (6.3%)	3 (25.0%)	4 (33.3%)	2 (14.3%)	-
Diarrhea	3 (18.8%)	-	1 (8.3%)	-	-	1 (7.1%)
Nausea	2 (12.5%)	-	3 (25.0%)	-	3 (21.4%)	-
Vomiting	3 (18.8%)	-	2 (16.7%)	-	3 (21.4%)	-
Asthenia/Fatigue	2 (12.5%)	-	5 (41.7%)	1 (8.3%)	3 (21.4%)	-
Pyrexia/Influenza-like Illness	**12 (75.0%)**	**1 (6.3%)**	**8 (66.7%)**	**-**	**12 (85.7%)**	**-**
Transaminase increases (ALT, AST)	2 (12.5%)	3 (18.8%)	1 (8.3%)	1 (8.3%)	2 (14.3%)	2 (14.3%)
Pancreatic enzyme increase (lipase, amylase)	1 (6.3%)	3 (18.8%)	-	-	-	-
Decreased appetite	3 (18.8%)	-	3 (25.0%)	-	-	-
Arthralgia	2 (12.5%)	-	-	-	-	-
Musculoskeletal pain	3 (18.8%)	-	4 (33.3%)	-	-	-
Dizziness	1 (6.3%)	-	1 (8.3%)	-	-	-
Headache	1 (6.3%)	-	1 (8.3%)	-	1 (7.1%)	-
Dyspnea	2 (12.5%)	-	-	-	-	-
Hypotension	2 (12.5%)	-	1 (8.3%)	-	-	-

*Part II: one patient at the highest dose ($1x10^{13}$ vp) died from a combination of thrombocytopenia (Grade 4) and enterocolitis (Grade 5)

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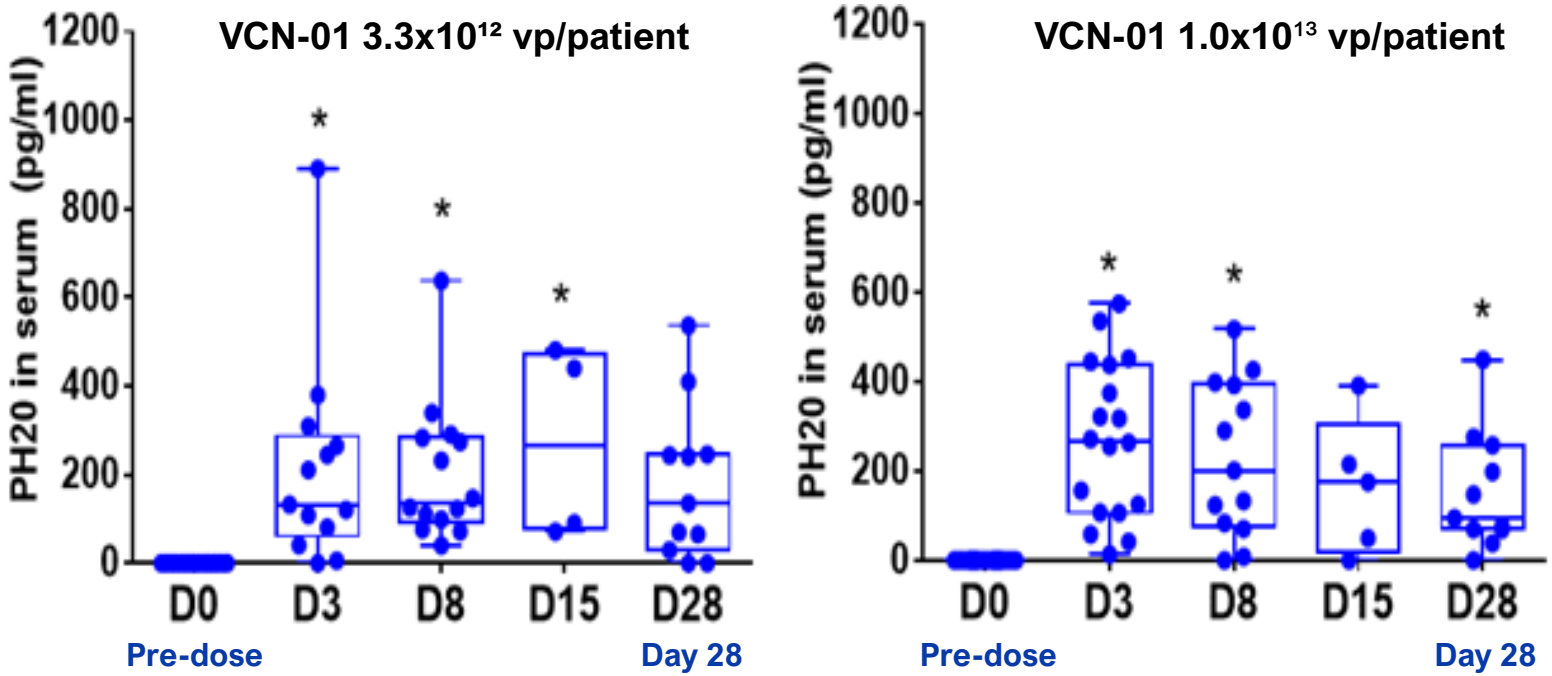
[1]NCT02045602. [2]Concomitant IV VCN-01 $3.3x10^{12}$ or $1.0x10^{13}$ vp/patient administered same day as first dose of SoC IV gemcitabine/nab-paclitaxel. [3]Sequential IV VCN-01 $3.3x10^{12}$ or $1.0x10^{13}$ vp/patient administered 7-days prior to first dose of SoC. Garcia-Carbonero (2022) J Immunother Cancer 10:e003255; data presented in part at ESMO 2019

PH20 is a Built-in Biomarker of VCN-01 Activity

Sustained PH20 levels in serum of PDAC patients treated with IV VCN-01



Hyaluronidase (PH20) levels in patient sera are linked to viral replication and demonstrate sustained VCN-01 activity in tumors

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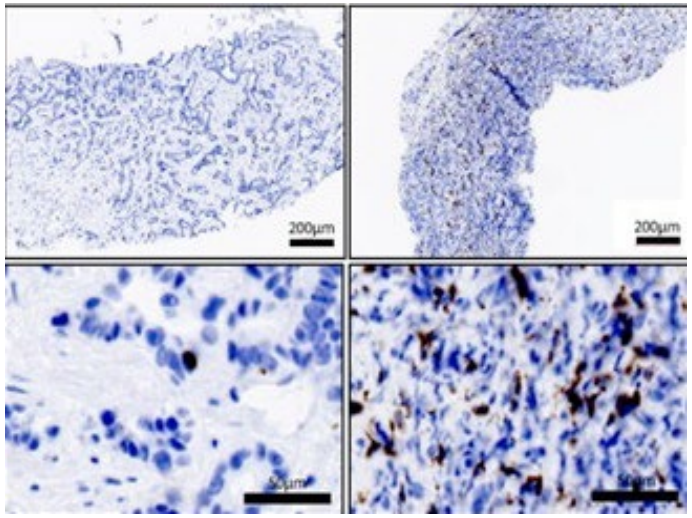
Garcia-Carbonero (2022) J Immunother Cancer 10:e003255; data presented in part at ESMO 2019.

VCN-01 Elicits an Anti-Tumor Inflammatory Response

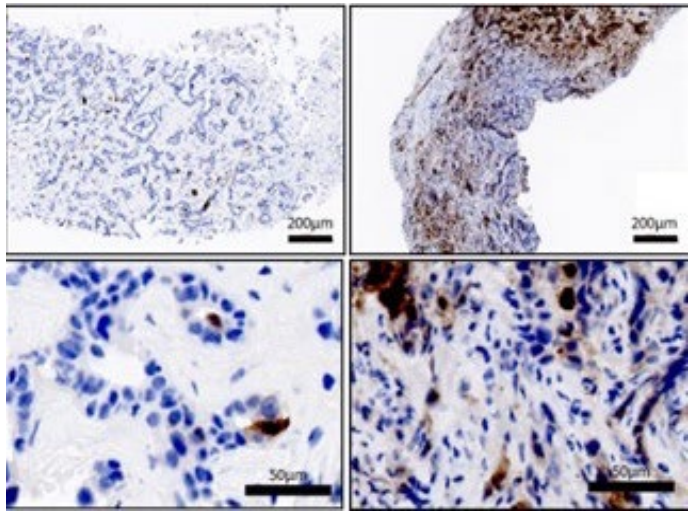
Remodels the tumor matrix and turns “cold” tumors “hot”

CD8⁺ lymphocyte infiltration



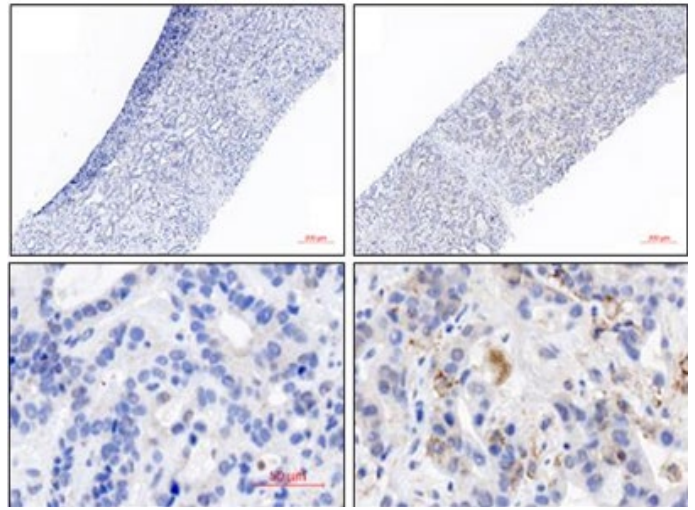
Pre-Dose Day 8

IDO upregulation



Pre-Dose Day 8

PD-L1 upregulation



Pre-Dose Day 8

Immunohistochemistry staining of biopsies from **hepatic metastases** of a PDAC patient treated with IV VCN-01

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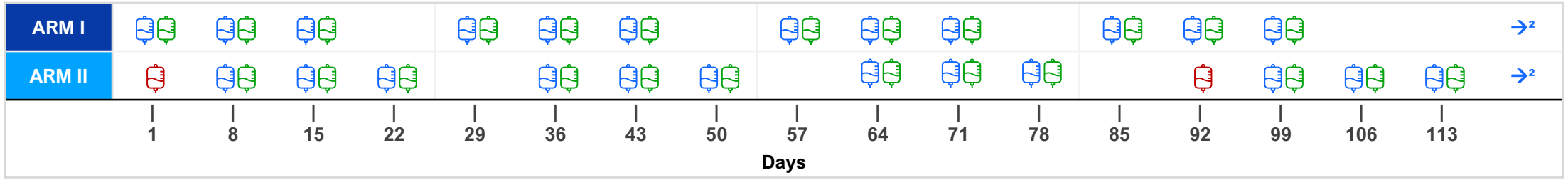
IDO indoleamine 2,3-dioxygenase. αPD-L1 programmed death-ligand 1. Garcia-Carbonero (2022) J Immunother Cancer 10:e003255; data presented in part at ESMO 2019.

VIRAGE Phase 2 Clinical Trial in PDAC

- 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: nab-paclitaxel/gemcitabine ( ) in 28-day cycles according to SoC
  - Arm II: VCN-01 ( ) IV administered 7-days before first dose of nab-paclitaxel/gemcitabine in Cycles 1 and 4



- Primary Endpoints
  - Time from randomization until death in both arms (overall survival; OS)
  - Safety and tolerability of IV VCN-01 administered at Week 1 and Week 14 in Arm II

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[1]VCN-01 1x10[13] vp by IV infusion (50 mL solution in NaCl 0.9%). [2]Continue SoC cycles until disease progression, intolerable/unacceptable toxicity, consent withdrawal or investigator's decision

VIRAGE Phase 2 Clinical Trial in PDAC

- Secondary Endpoints (interim opportunity to evaluate potential VCN-01 effects)
  - Time to progression (TTP) or progression free survival (PFS)
  - Objective Response rate (ORR), Disease control rate (DCR), Duration of response (DoR)
  - Landmark 1-year survival and PFS at the 1-year landmark
- Exploratory Endpoints
  - Systemic markers of VCN-01 pharmacokinetics and immune response[2]
  - Radiomic analysis of computerized tomography (CT) images; Quality of Life (QoL)
- Status
  - ✓Protocol given permission to proceed in Spain and USA (finalizing process in Germany)
  - ✓Orphan Drug Designation in EU (application to be submitted in USA)
  - ✓PI Dr. Manuel Hidalgo Medina, MD PhD[1]
  - ✓Anticipate trial initiation Q4 2022

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[1]Chief of the Division of Hematology and Medical Oncology at Weill Cornell Medicine/New York-Presbyterian Hospital. [2]Circulating immune markers in serum, VCN-01 genomes in blood, PH20 levels in serum, neutrophil/lymphocyte ratio, and serum levels of neutralizing anti-VCN-01 antibodies (Anti-Ad-NAbs)

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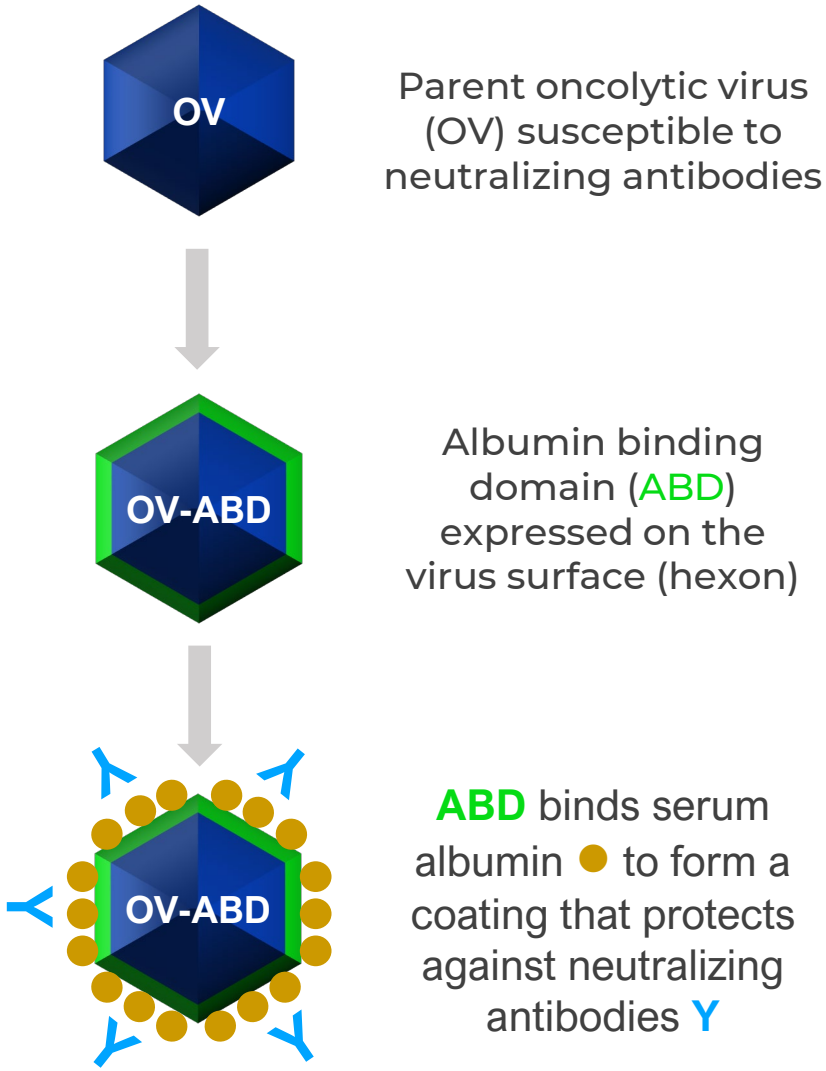
Opportunities for Long Term Growth

Albumin Shield™ to Enhance OV Systemic Delivery

- Albumin Shield technology protects OVs as they travel to tumors after systemic administration[1,2]
- Albumin Shield modified OVs bind albumin in the patient's blood to form a protective coating
- Albumin Shield genetic modification allows parent and progeny virus to be albumin coated
- Albumin Shield may enable multiple IV administrations for hard-to-treat patients
- Albumin Shield first candidate VCN-11 is being prepared for a potential Phase 1 clinical trial



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[1]Rojas (2016) J Control Rel 237:78; ABD binds mouse and human serum albumin, but not bovine; [2]Mato-Berciano (2021) J Control Rel 332:517.

Theriva OV Pipeline Discovery and Development

Advancing company founders' decades of world leading OV innovation

Common Features

Clinically-tested Adenovirus Expressing PH20 Hyaluronidase TO DEGRADE Stroma

+

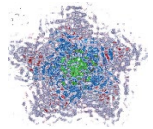
Albumin Shield™
To Prevent Neutralization By Circulating Anti-viral Antibodies To Facilitate IV Multidosing

+

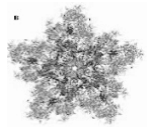
Unique Multifunctional Proteins
To Turn Cold Tumors Hot

Product Specific Features

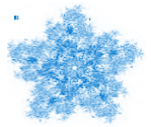
VCN-11 Hyaluronidase alone



VCN-12 Hyaluronidase + Toxins



VCN-13 Fusion Hyaluronidase + scPD-L1



VCN-XX Hyaluronidase + other payloads

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Theriva Value-Generating OV Pipeline

VCN-11 "armed" with transgenes to vary function, expand efficacy

DISCOVERY

- Alternate Therapeutic Targets
- New Indications
- New Combinations
- **Long-Term Value Generation**

VCN-01 with added Albumin Shield™ to evade NAbs, enable repeat dosing

PRE-IND

- New Dosing Regimens
- New Indications
- New Combinations
- **VCN-01 Lifecycle Management**

Systemic, Selective, Stroma degrading, Highly Replicating, oncolytic AdV5

PHASE 2

- Multiple Potential Value Opportunities
- Indications (*PDAC, Retinoblastoma, HNSCC ...*)
- Combinations (*Chemotherapy, CAR-T, CPI*)
- **Nearest Term Commercial Opportunity**

Clinical validation expected to facilitate portfolio partnering

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Corporate Summary

Intellectual Property

Hyaluronidase OV

VCN-01, VCN-11

Composition of Matter (exp 2030)

Methods of Use and Novel Formulations (examination)

Use in Rb (exp 2036)

ODD EU (PDAC)

ODD US (Rb)

Albumin Shield™

VCN-11, Discovery

Composition of Matter (exp 2034)

Methods of Use and Novel Formulations (examination)

Oral β-Lactamase

SYN-004, -006, -007

Composition of Matter (exp 2031-5)

Methods of Use and Novel Formulations (exp 2035-6)

Oral IAP

SYN-020

Manufacturing Know-how (Trade Secret)

Methods of Use and Novel Formulations (applications filed)

Option to additional IP from MGH

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ODD Orphan Drug Designation provides 7 years market exclusivity in US and 10 years in the EU. OV oncolytic virus. PDAC pancreatic ductal adenocarcinoma. Rb retinoblastoma.

Financial Snapshot

Exchange	NYSE American
Ticker	TVOX
Current Cash (as of 06/30/2022)	$50.5 million
Average Daily Volume (3M Ave)	~75K
Locations	Rockville, MD Barcelona, Spain

Near Term and Projected News Flow

Q3 2022

- SYN-004 Phase 1b/2a data 1st cohort
- Theriva Biologics rebranding

Q4 2022

- VCN-01 PDAC Phase 2 1st patient dosed Spain
- SYN-004 Phase 1b/2a 2nd cohort dosing
- VCN-01 investigator sponsored study U. Leeds 1st patient dosed
- *LifeSci VCN-01 PDAC KOL event*

H1 2023

- VCN-01 PDAC Phase 2 study 1st patients dosed USA, Germany
- FDA meeting VCN-01 retinoblastoma program
- VCN-01 investigator sponsored study HNSCC survival data
- *JP Morgan, AACR, ASGCT, ASCO, ECCMID*

H2 2023 Q1 2024

- VCN-01 retinoblastoma clinical trial initiation[1]
- VCN-11 IND Filing[1,2]
- VCN-12 candidate selection[3]
- VCN-01 retinoblastoma clinical trial initiation[1]
- VCN-01 PDAC Phase 2 interim data
- SYN-004 Phase 1b/2a data 2nd cohort

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[1]Contingent on appropriate funding and VCN-01 clinical trials progress. [2]VCN-11 is the first clinical candidate using the Albumin Binding Domain™ technology. [3]VCN-12 is an armed version of VCN-11 designed to express an additional functional payload.

Investment Highlights

Positioned at the forefront of oncolytic virus (OV) development

Unique, clinical-stage OV (VCN-01) optimized for systemic administration, selective tumor destruction, and enhancement of chemotherapy and immunotherapy

Expanding the pipeline with a next-generation OV that incorporates Albumin Shield™ technology (VCN-11) designed for hard-to-treat cancers

Multiple near-term catalysts

Lead product VCN-01 poised to enter a Phase 2 clinical study in metastatic pancreatic ductal adenocarcinoma and a Company sponsored study in retinoblastoma

Advancing SYN-004 in ongoing clinical trials

Accelerating the path to value

VCN-01 received Orphan Drug Designation (ODD) for retinoblastoma from the U.S. FDA and ODD by the EMA for pancreatic cancer

Established footprint in EU market for discovery and clinical development, partnering, and commercialization

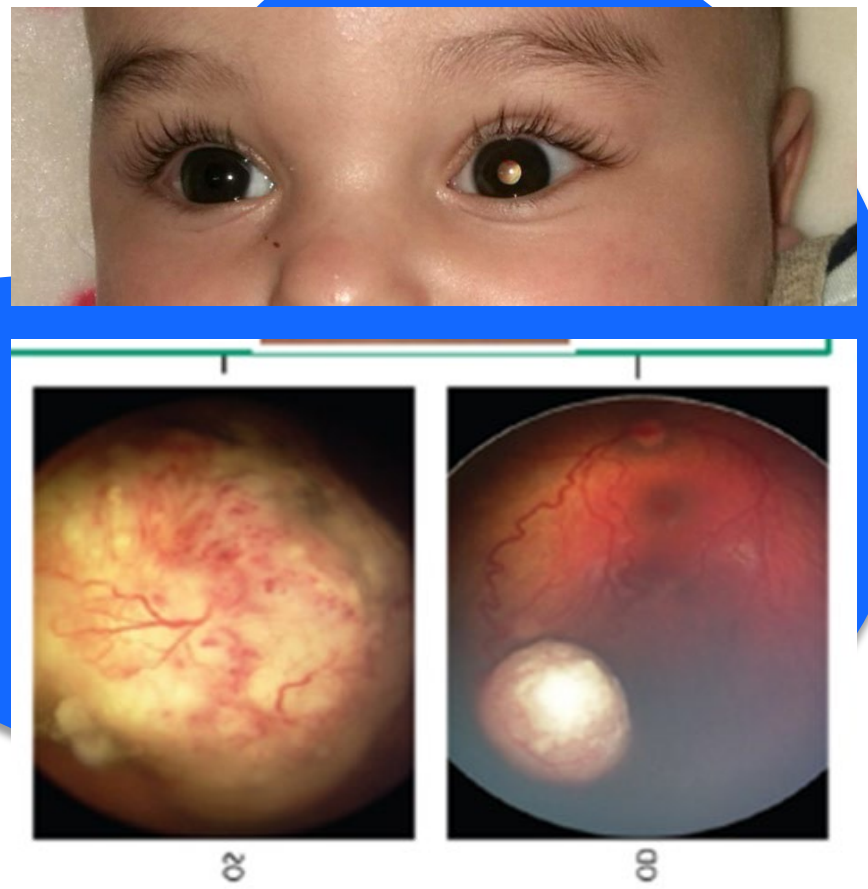
Collaborations with leading research and academic institutions

Appendix

VCN-01 Clinical Program in Retinoblastoma

Retinoblastoma, a Rare Pediatric Malignancy

- Retinoblastoma (Rb) is an orphan indication that accounts for ~2-3% of all childhood cancers[1]
- 200-300 cases each year in the USA, EU[2-4]
- VCN-01 selectivity enables development as an intravitreal treatment for Rb patients
- VCN-01 could be used in combination with chemotherapy to potentially improve outcomes
- VCN-01 could be used as a rescue therapy for patients who fail standard therapy



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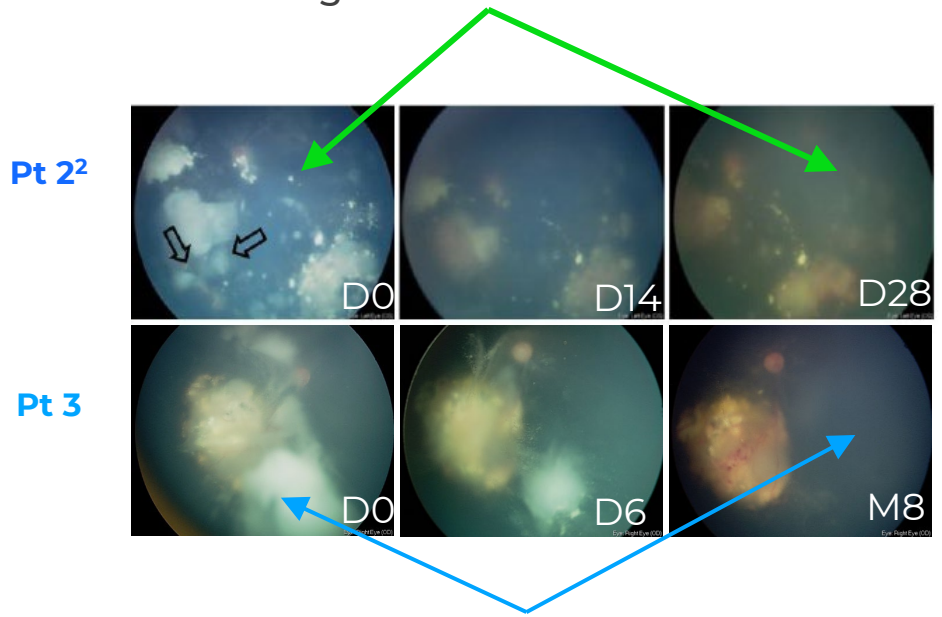
[1]https://www.cancer.org/cancer/retinoblastoma/about/key-statistics.html. [2]Stacey (2021) Ophthalmology 128:1369. [3]One Retinoblastoma World Map https://map.1rbw.org/. [4]For additional details and references see Appendix. IMAGE: Courtesy of Hospital Sant Joan de Déu, Barcelona

VCN-01 in Retinoblastoma

- On-going single center, open-label, dose escalation study of intravitreal (IVit) VCN-01[1-3]
  - Children aged 1-12 years (n=6 to date)
  - Retinoblastoma that is recurrent or refractory to chemotherapy and for whom enucleation is the best treatment option
  - VCN-01 doses of $2.0x10^9$ vp per eye (n=1) or $2.0x10^{10}$ vp per eye (n=4) on days 1 and 15
- Promising antitumor activity and appropriate safety and tolerability at RP2D
  - Enucleation avoided in 1 of 4 patients to date
  - Low VCN-01 dose and/or damage from prior chemotherapy meant eye could not be saved in 3 patients
- Earlier VCN-01 intervention anticipated to have better outcomes

Promising Results in 2 of the 3 Patients Treated to Date with High Dose VCN-01

Reduced number and size of tumor vitreous seeds following VCN-01 administration[2]



Complete tumor regression[3]

[1]NCT03284268. [2]Pascual Pasto (2019) Sci Transl Med 11:eaat9321. [3]Data presented at International Oncolytic Virus Conference IOVC2021, 07 November 2021, Sedona, AZ. Link to IOVC2021 slide deck provided in Appendix. RP2D recommended phase 2 dose. vp virus particles.

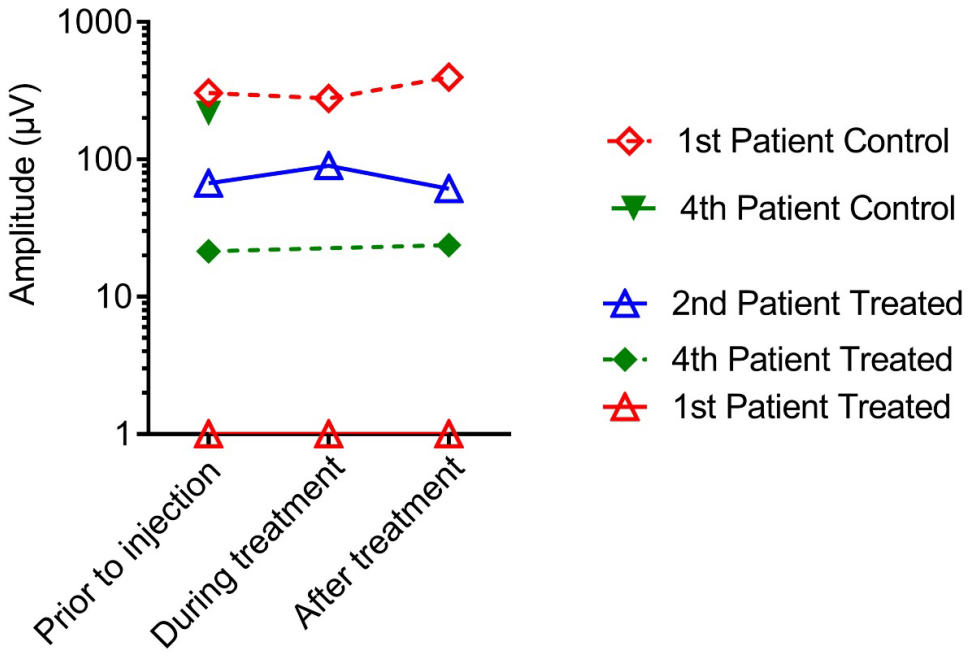
Interim Safety Data for Intravitreal VCN-01

Two Intravitreal VCN-01 Doses of $2.0x10^9$ or $2.0x10^{10}$ vp per eye[1]

Adverse Reaction	Pts	All Grades		Grade ≥3	
CTCAE grade	N	n	%	n	%
Uveitis	4	2	50%	2	50%
Periphlebitis	4	1	25%	0	0%

- VCN-01 was reasonably well tolerated after intravitreal administration[2], although some turbidity and vitritis associated with intravitreal inflammation was observed
- Intravitreal inflammation was managed with local and systemic administration of anti-inflammatory drugs
- VCN-01 did not appear to change retinal function (electroretinographic signaling)
- VCN-01 does not replicate in healthy retinal tissue[3]

Stable Electroretinographic Signals



[1]NCT03284268. [2]Intravitreal VCN-01 doses of $2.0x10^9$ virus particles (vp) per eye (Patient 1) or $2.0x10^{10}$ vp per eye (Patients 2-4) administered on days 1 and 15. [3]Pascual Pasto (2019) Sci Transl Med 11:eaat9321. Data presented at International Oncolytic Virus Conference IOVC2021, 07 November 2021, Sedona, AZ.

Retinoblastoma Project Clinical Development

- Developing a clinical protocol for an open-label, multinational study
  - Rb patients with vitreous seeds
  - IVit VCN-01 in combination with IVit chemotherapy (no defined SoC)
  - PI Dr. Guillermo Chantada, MD PhD[1]
- Status
  - Clinical study design being discussed with KOLs
  - Analyzing regulatory landscape and recruitment rates in different geographical regions
  - US Orphan Drug Designation
  - Anticipate trial initiation late 2023 (contingent on regulatory agreement)

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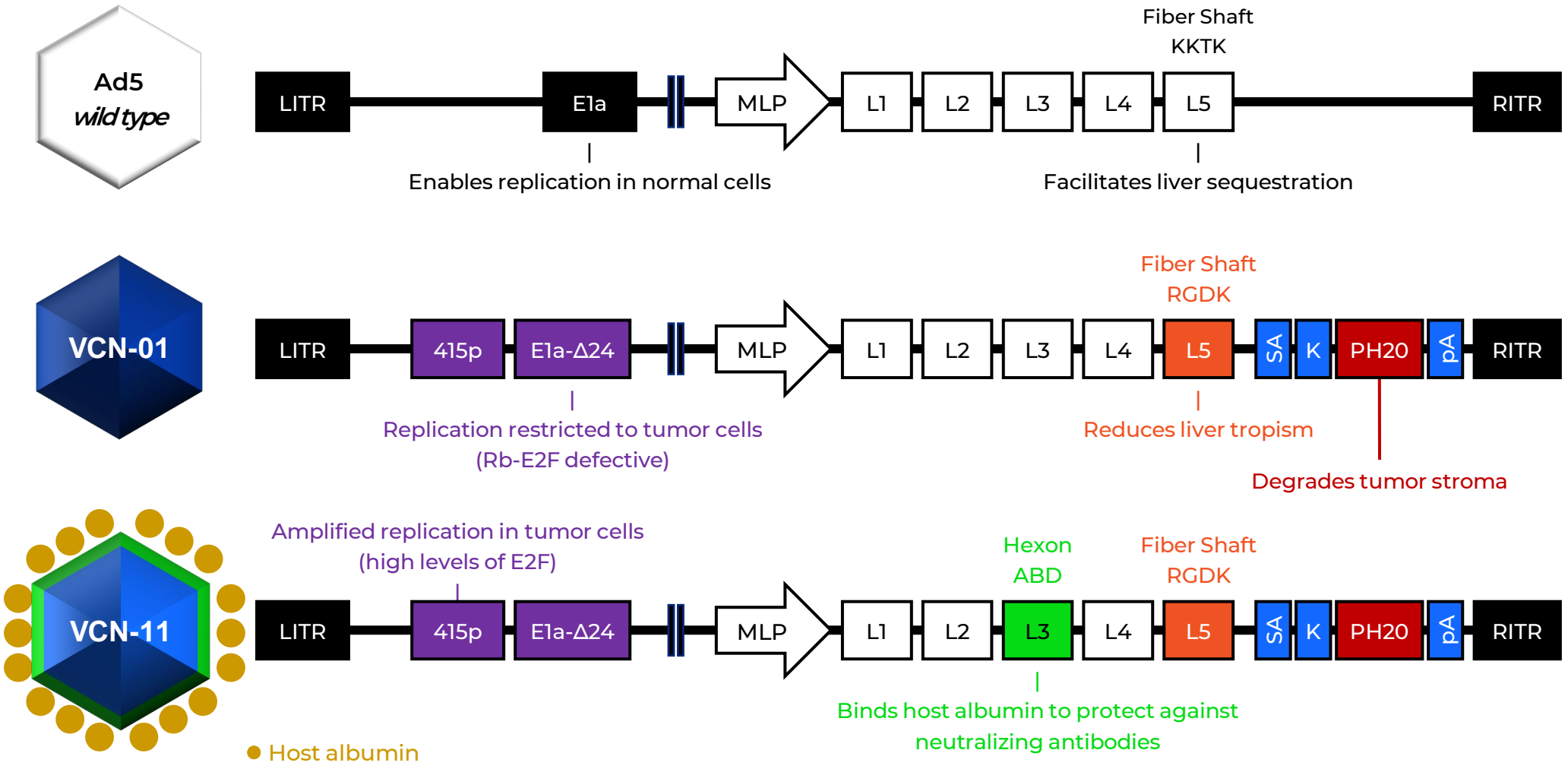
[1]Principal Researcher, Associate Physician, Hospital Sant Joan de Déu, Barcelona, Spain; Scientific Director, Pediatric Hemato-Oncology Service of the Hospital Universitario Austral, Argentina

VCN Oncolytic Virus Genetic Modifications



ABD albumin binding domain (streptococcal protein G)[1]

Ad5 Adenovirus type 5

E1a-Δ24 deletion of 24 base pairs within the E1a promoter; further modified by insertion of 8 extra E2F binding sites and one Sp1-binding site at nucleotide site 415 (415p)

MLP major late promoter[2]

PH20 soluble human testicular hyaluronidase[3]

KKTK Lys-Lys-Thr-Lys putative HSPG binding domain on fiber shaft

RGDK Arg-Gly-Asp-Lys inserted in place of KKTK on fiber shaft

VCN-12 VCN-11 armed with additional therapeutic transgene

[1]Since this is a transgene, progeny virus will also be albumin coated. [2]MLP control means transgenes will only be expressed after replication, which occurs selectively in tumor cells. Transgene expression (PH20 in blood) can be a biomarker for viral replication in the tumor. [3]PH20 cassette inserted downstream of the fiber gene contains a splice acceptor (SA), a kozak sequence (K) and a polyadenylation stop sequence (pA)

VCN-01 Clinical Summary

Extensive Phase 1 Clinical Experience

- Administered to 77 cancer patients to date (61 by IV dosing)
- Alone or in combination with chemotherapy, immunotherapy

Clinical Demonstration of MOA

- High levels of viral replication and PH20 expression in tumors
- Increased tumor immunogenicity and tumor inflammation

Strong Support for Phase 2 Trials

- Tumor responses in PDAC and Rb patients treated with VCN-01
- Appropriate VCN-01 safety and tolerability for patient population
- Favorable survival in PDAC patients treated with VCN-01 plus SoC chemotherapy compared to published data for SoC alone

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SoC Standard of Care (gemcitabine/nab-paclitaxel)

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VCN-01 Clinical Program
Phase 1 Trial in Head & Neck Squamous Cell Carcinoma

NCT03799744 : Systemic VCN-01 in HNSCC & Durvalumab (α-PD-L1)

Design

Pre-screening for anti-hAd5 neutralizing antibodies (65-70% recruiting rate at selected threshold)

ARM I

VCN-01 in combination with Durvalumab Concomitant schedule

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

C-2
single dose
1E13 vp /patient

3+3 Dose escalating Design

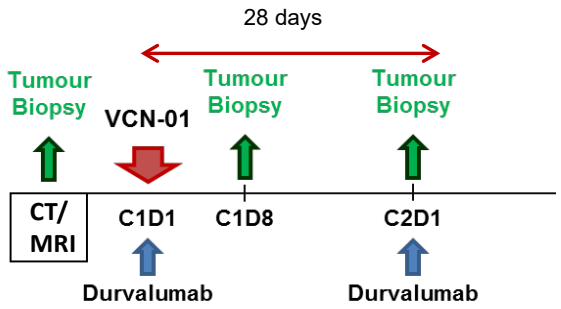
ARM II

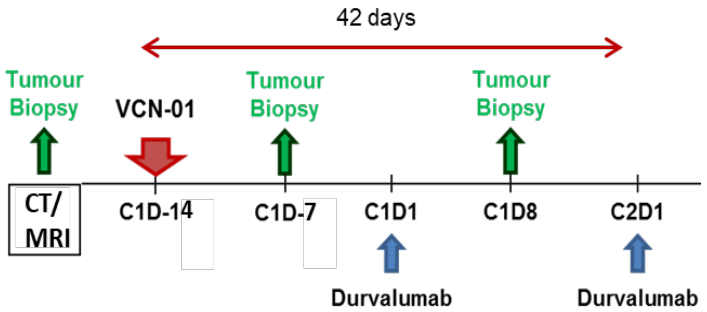
VCN-01 in combination with Durvalumab in a Sequential schedule

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

S-2
single dose
1E13 vp /patient

3+3 Dose escalating Design





Study Population:

Patients with metastatic squamous cell carcinoma of the head & neck previously treated with anti-PD(L)1 agents (R/MHNSCC)

Sites:

ICO Institut Català d'Oncologia

VHIO VALL D'HEBRON Institut d'Oncologia

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NCT03799744: Systemic VCN-01 in HNSCC & Durvalumab (α-PD-L1)

Most Common IV VCN-01 Related AEs (IV in HNSCC + Durvalumab)

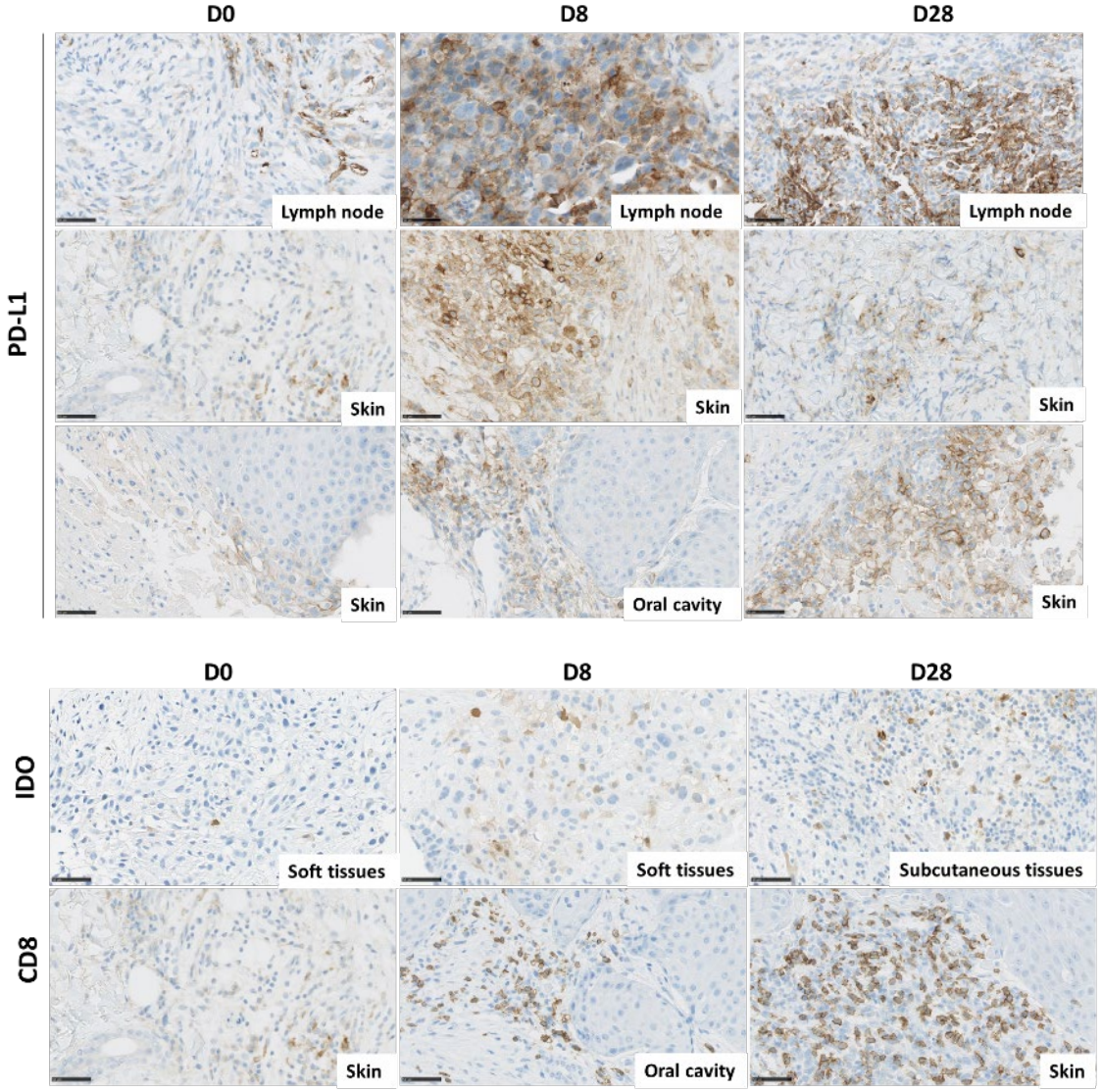
Adverse Reactions	Arm I (Concomitant, 6)[2]		Arm II (Sequential, 14)[3]	
CTCAE Grade	Grade 1-2	Grade ≥3	Grade 1-2	Grade ≥3
Pyrexia	2 (33,0%)	-	8 (57,1%)	-
Influenza like illness	3 (50,0%)	-	5 (35,7%)	2 (14,2%)
Asthenia/Fatigue	2 (33.0%)	-	6 (42,8%)	1 (7,1%)
AST increased	4 (66,7%)	1 (16,6%)	3 (21,4%)	-
ALT increased	3 (50,0%)	1 (16,6%)	2 (14,2%)	-
Decreased Apetite	1 (16,6%)	-	4 (35,7%)	-
Lymphocyte count decreased	1 (16,6%)	-	-	3 (21,4%)
Myalgia	-	-	4 (35,7%)	-
Hypotension	-	-	3 (21,4%)	-
Chills	1 (16,6%)	-	2 (14,2%)	-
Vomiting	1 (16,6%)	-	2 (14,2%)	-
Anemia	2 (33,0%)	-	1 (7,1%)	-
Nausea	-	-	2 (14,2%)	-
Headache	-	-	2 (14,2%)	-
Erythema	1 (16,6%)	-	1 (7,1%)	-
Hepatic Function Abnormal	-	1 (16,6%)	-	-
Guillain-Barre Syndrome	-	-	-	1 (7,1%)
Hepatic enzymes increased	-	-	-	1 (7,1%)
GGT Increased	-	-	-	1 (7,1%)

NCT03799744 : Analysis of MoA in Clinical Samples

VCN-01 induces up-regulation of PD-L1 in tumor cells

	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



VCN-01 could favor pembrolizumab prescription in 1st line metastatic SSCHN for patients with CPS <1

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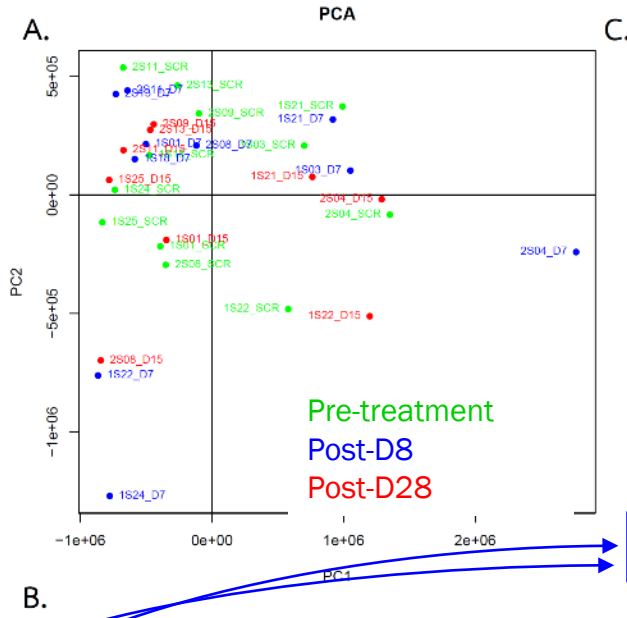
Trial NCT03799744 : Analysis of MoA in Clinical Samples

VCN-01 induces Transcriptomic Changes in Tumor Microenvironment

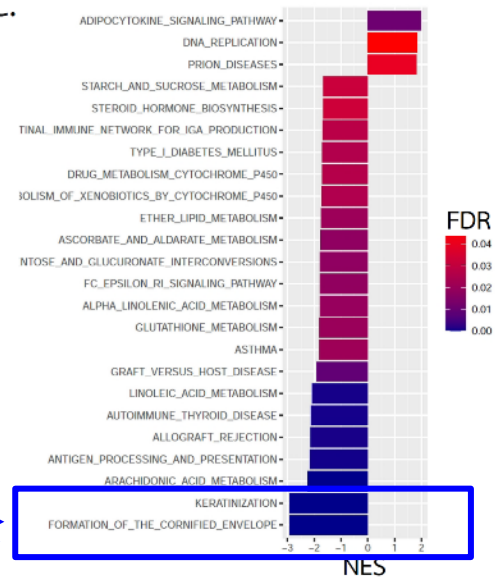
Principal Component Analysis[1]

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

NCT03799744 : Analysis of MoA in Clinical Samples

Perfusion changes induced by VCN-01

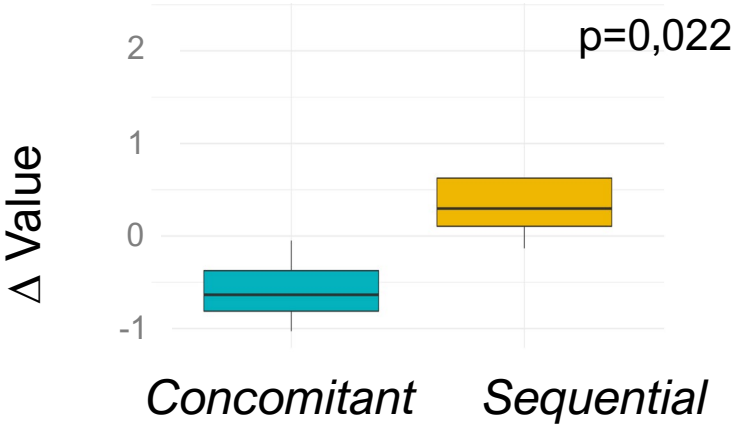
Dynamic contrast enhanced (DCE) were acquired from MRI images in Trial NCT03799744 (Systemic VCN-01 in HNSCC & Durvalumab[1]

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)



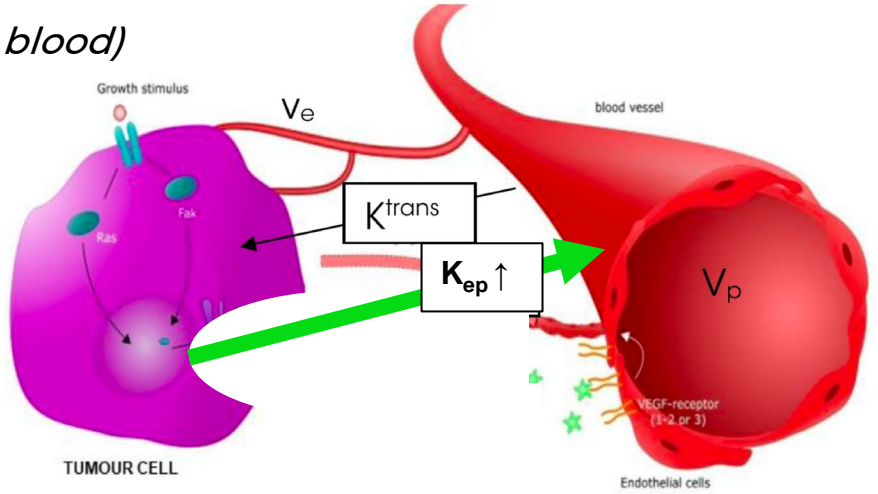


Figure 1. Pharmacokinetic perfusion model

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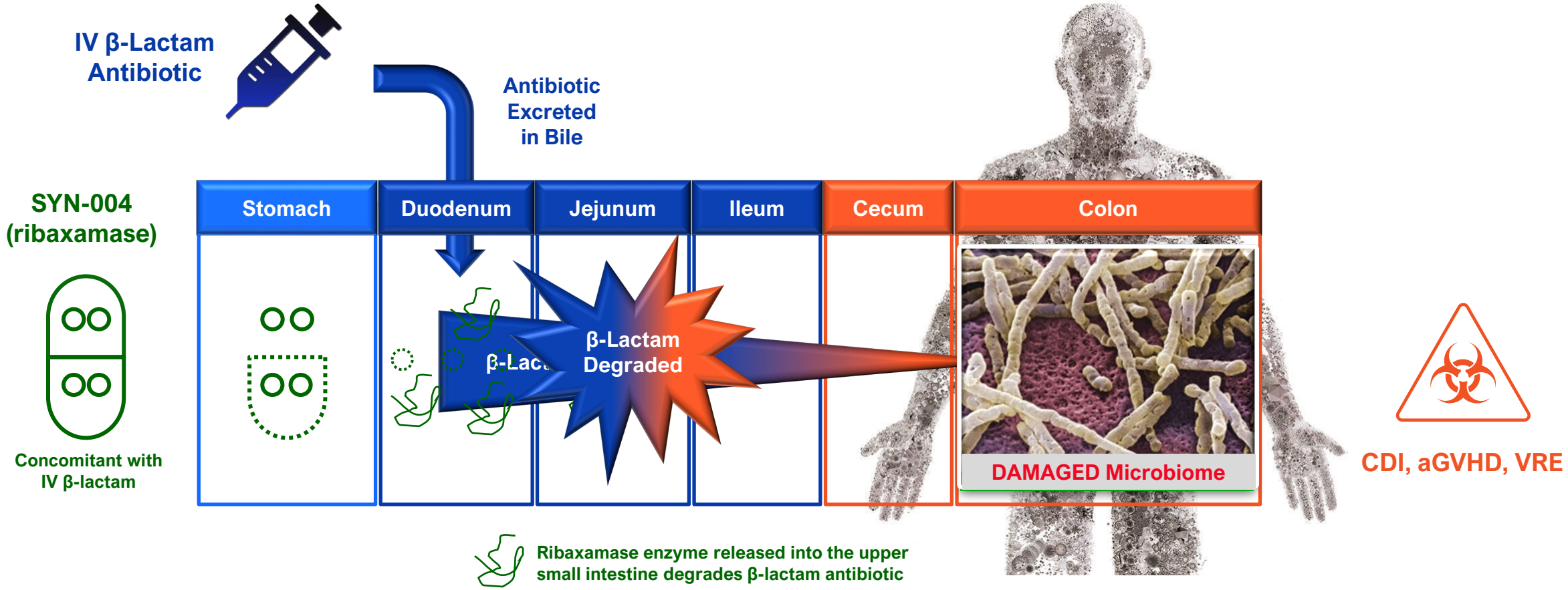
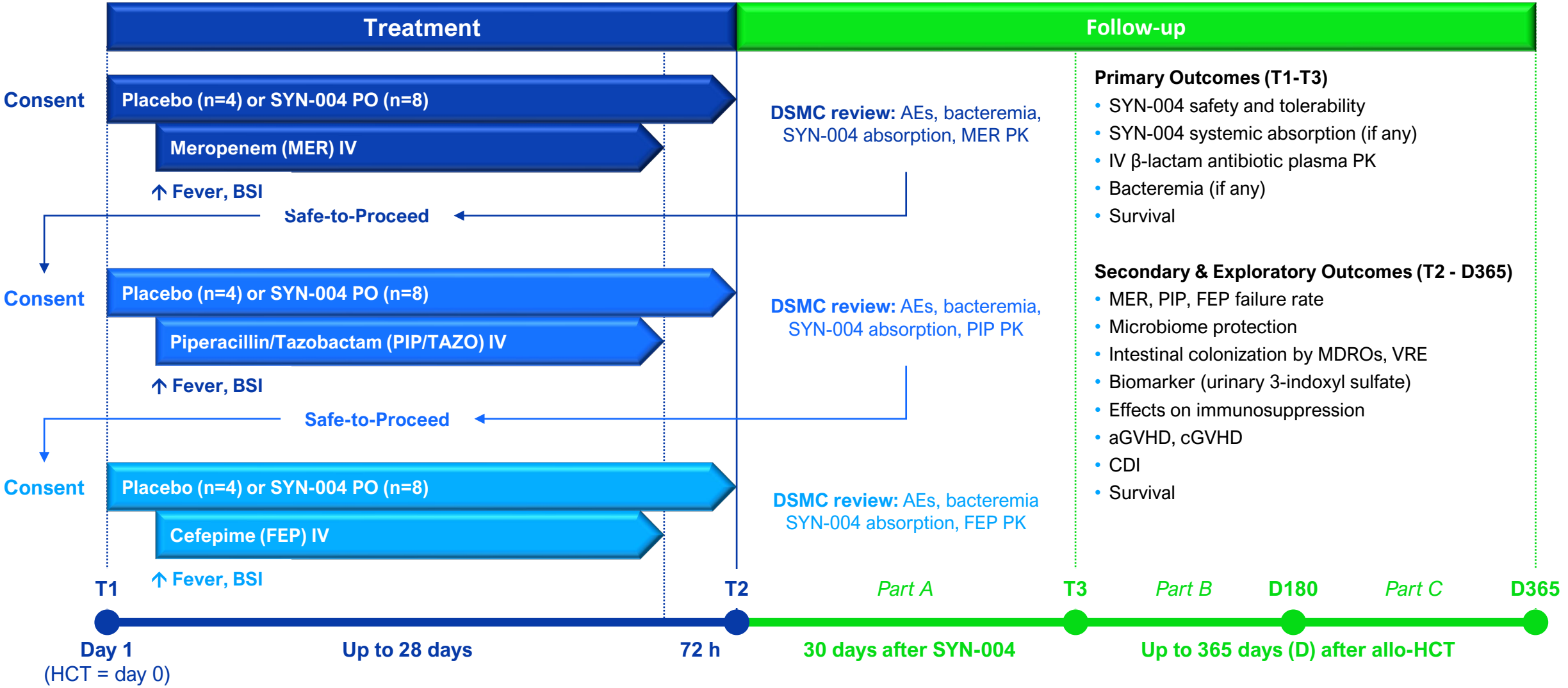
SYN-004 (ribaxamase)

SYN-004 (ribaxamase) to Prevent Microbiome Damage

Preserving the gut microbiome to prevent disease



SYN-004 in Allo-HCT Patients Phase 1b/2a Study SB-1-004-006



aGVHD (cGVHD) acute (chronic) graft-versus-host-disease. Allo-HCT allogeneic hematopoietic cell transplant. CDI Clostridioides difficile infection. DSMC data safety and monitoring committee. MDRO multidrug resistant organism. VRE vancomycin resistant enterococci

SYN-004 in Allogeneic HCT Patients Study Update (1 of 2)

- Completed Cohort 1 of 3 and proceeding to Cohort 2
  - 19 patients in Cohort 1 received at least one dose of study drug (SYN-004 or Placebo)
  - 16 patients received at least one dose of IV meropenem
  - 12 patients completed at least two meropenem PK periods and were evaluable towards the endpoints
- AEs and SAEs observed in Cohort 1 were typical for allo-HCT patients
  - AEs or SAEs were determined to be unrelated to study drug treatment by the investigators
  - A total of 29 severe TEAEs were reported among 12 participants (including 13 SAEs among 10 participants) most commonly infections/infestations including sepsis (Appendix)[1]
- One patient died 14 days after the last dose of study drug due to sepsis that was unrelated to study drug[2]
  - Two patients died 72 days and 114 days after the last dose of study drug due to cancer relapse that was unrelated to study drug

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[1]Severe AE is CTCAE grade ≥3. [2]Within the protocol-specified 30-day reporting period. Allo-HCT allogeneic hematopoietic cell transplant. (S)AE (serious) adverse event. TEAE treatment emergent adverse event.

SYN-004 in Allogeneic HCT Patients Study Update (2 of 2)

- Consistent with studies in healthy volunteers, SYN-004 was not observed in plasma samples from the majority of patients
  - A total of 3 plasma samples had low but quantifiable SYN-004 levels (sensitive ECL assay)
  - No active SYN-004 enzyme was detected in these samples (functional activity assay)(Appendix)
- Meropenem pharmacokinetics were as expected for this patient population
  - Meropenem is not metabolized by SYN-004; PK sampling will be expanded in Cohorts 2 and 3
- DSMC convened on 20Sep2022 and recommended initiation of Cohort 2
  - Asked for more information about sepsis events but did not request protocol amendments
- Protocol amendment submitted to WU IRB 22Sep2022
  - Refine antibiotic PK sampling and monitoring of aGVHD prophylaxis/immunosuppressants
  - Assuming no IRB concerns, patient recruitment for Cohort 2 should start mid-to-late October

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Allo-HCT allogeneic hematopoietic cell transplant. DSMC Data and Safety Monitoring Committee. ECL electrochemiluminescence.

•. 2021 Feb 1;27(3):889-902.
•. 2021 Feb 1;27(3):889-902.

VCN Oncolytic Viruses Key Publications

Bayo-Puxan N et al. (2006) Role of the putative heparan sulfate glycosaminoglycan-binding site of the adenovirus type 5 fiber shaft on liver detargeting and knob-mediated retargeting. *J Gen Virol* 87:2487–2495

Bazan-Peregrino M et al. (2021) VCN-01 disrupts pancreatic cancer stroma and exerts antitumor effects. *J ImmunoTher Cancer* 9:e003254.

Garcia-Carbonero R et al. (2019) Poster 5185: Systemic administration of the hyaluronidase-expressing oncolytic adenovirus VCN-01 in patients with advanced or metastatic pancreatic cancer: first-in-human clinical trial. European Society for Molecular Oncology conference ESMO 2019, 29 September 2019, Barcelona, Spain.

Garcia-Carbonero R et al. (2022) A phase I, multicenter, open-label study of intravenous VCN-01 oncolytic adenovirus with or without nab-paclitaxel plus gemcitabine in patients with advanced solid tumors *J ImmunoTher Cancer* 10:e003255

Hidalgo M et al. (2019) Poster 5465: Proof of concept clinical study by EUS-guided intratumor injection of VCN-01, an oncolytic adenovirus expressing hyaluronidase in patients with pancreatic cancer. European Society for Molecular Oncology conference ESMO 2019, 28 September 2019, Barcelona, Spain.

Kiyokawa M et al. (2021) Modification of Extracellular Matrix Enhances Oncolytic Adenovirus Immunotherapy in Glioblastoma. *Clin Cancer Res* 27:889-902

Martínez-Vélez N et al. (2019) The oncolytic adenovirus VCN-01 as therapeutic approach against pediatric osteosarcoma. *Clin Cancer Res* 22:2217-25

Mato-Berciano A et al. (2021) Oncolytic adenovirus with hyaluronidase activity that evades neutralizing antibodies: VCN-11. *J Control Rel* 332:517-528

Pascual Pasto G et al. (2019) Therapeutic targeting of the RB1 pathway in retinoblastoma with the oncolytic adenovirus VCN-01. *Sci Transl Med* 11:eaat9321

Pascual-Pasto G et al. (2021) Presentation: VCN-01 is an encouraging therapy against retinoblastoma. International Oncolytic Virus Conference IOVC2021, 07 November 2021, Sedona, AZ.

Rodríguez-García A et al. (2015) Safety and efficacy of VCN-01, an oncolytic adenovirus combining fiber HSG-binding domain replacement with RGD and hyaluronidase expression. *Clin Cancer Res* 21:1406-18

Rojas J et al. (2012) Improved systemic antitumor therapy with oncolytic adenoviruses by replacing the fiber shaft HSG-binding domain with RGD. *Gene Ther* 19:453–457

Rojas LA et al. (2016) Albumin-binding adenoviruses circumvent pre-existing neutralizing antibodies upon systemic delivery. *J Control Rel* 237:78–88

Pancreatic Cancer References

DESCRIPTION, CLASSIFICATION, STAGING, STROMA

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