Synthetic BIOLOGICS

VCN BIOSCIENCES

B. Riley Securities Oncology Investor Conference

January 2022

Forward-Looking Statements

This presentation includes forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995, as amended, concerning Synthetic Biologics and VCN Biosciences ("VCN") . In some cases forward-looking statements can be identified by terminology such as "may," "should," "potential," "continue," "expects," "anticipates," "intends," "plans," "believes," "estimates," "indicates," and similar expressions. These statements are based upon management's current beliefs, expectations and assumptions and are subject to a number of risks and uncertainties, many of which are difficult to predict and include statements regarding the proposed acquisition of VCN by Synthetic Biologics, the timing of such acquisition and the various timelines for development of VCN's product candidates. The forward-looking statements are subject to risks and uncertainties that could cause actual results to differ materially from those set forth or implied by any forward-looking statements. Important factors that could cause actual results to differ materially from those reflected in Synthetic Biologics' forward-looking statements include, among others, the risk associated with Synthetic Biologics' and VCN's ability to satisfy the conditions to consummate the proposed acquisition, including obtaining necessary governmental approvals, the timing of the closing of the proposed acquisition, the occurrence of any event, change or other circumstance or condition that could give rise to the termination of the Stock Purchase Agreement between the shareholders of VCN and Synthetic Biologics, unanticipated difficulties or expenditures relating to the proposed acquisition or development of VCN's drug candidates, the response of business partners and competitors to the announcement of the proposed acquisition, and/or potential difficulties in employee retention as a result of the announcement and pendency of the proposed acquisition, whether the combined business of Synthetic Biologics and VCN will be successful, Synthetic Biologics' and VCN's product candidates demonstrating safety and effectiveness, as well as results that are consistent with prior results, the ability to initiate clinical trials and if initiated, the ability to complete them on time and achieve the desired results and benefits continuing 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 Synthetic Biologics' and VCN's 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 Synthetic Biologics' and VCN's products, developments by competitors that render such products obsolete or non-competitive, Synthetic Biologics' and VCN's ability to maintain license agreements, the continued maintenance and growth of Synthetic Biologics' and VCN's patent estate, and other factors described in Synthetic Biologics' annual report on Form 10-K for the year ended December 31, 2020, subsequent quarterly reports on Form 10-Qs and any other filings we make with the SEC. Synthetic Biologics can give no assurance that the conditions to the acquisition will be satisfied. The information in this presentation is provided only as of the date presented, and Synthetic Biologics undertakes no obligation to update any forward-looking statements contained in this presentation on account of new information, future events, or otherwise, except as required by law.

Synthetic Biologics and VCN Biosciences S.L.

- Synthetic Biologics (NYSE American: **SYN**) advancing into oncology with the acquisition of Barcelona-based VCN Biosciences S.L.
  - Transaction announced 14 December 2021 (closing subject to conditions including Spanish government approval)[1]
- VCN is developing unique oncolytic viruses (**OVs**) optimized for **intravenous** administration and maximum tumor destruction
- Lead clinical product **VCN-01** poised to enter a Phase 2 clinical study in patients with newly-diagnosed metastatic pancreatic ductal adenocarcinoma (**PDAC**) and a Phase 2/3 study in retinoblastoma
- Compelling platform of next-generation OVs (**VCN-11 family**) designed to address additional hard-to-treat cancers with high unmet need

[1]Foreign direct investment (FDI) approval anticipated within 60 days from signing.

SYN-VCN Transaction Summary

- Synthetic Biologics (NYSE American: **SYN**) to acquire 100% outstanding equity of VCN
  - Total **upfront** consideration for the acquisition is $4.7M in cash
  - Shares of SYN common stock equal to 19.99% of the outstanding shares of common stock distributed to VCN
- Up to $70.25M total cash milestone payments
  - **Backend loaded** predominantly based on future Phase 2/3 clinical and regulatory milestones
  - No royalties or commercial sales milestones to sellers
- VCN to maintain current legal structure, operate as a wholly owned subsidiary of SYN
- Closing subject to conditions including Foreign Direct Investment (FDI) approval by the Spanish government[1]

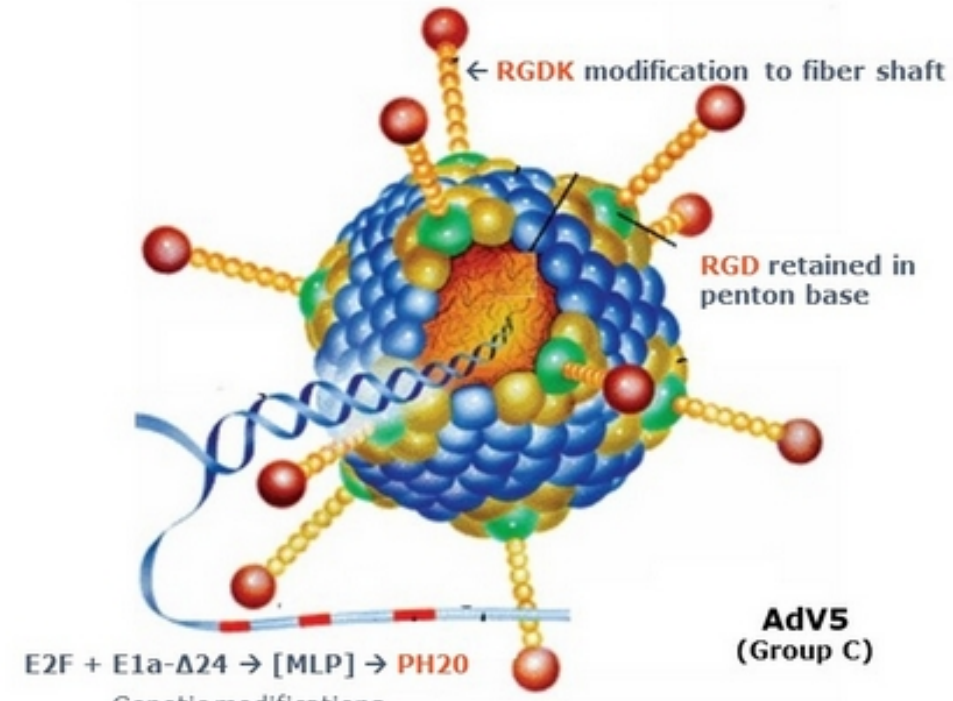
[1]FDI approval anticipated within 60 days from signing.

Oncolytic Virus Features and Challenges

- **OVs are a Promising Cancer Therapeutic Approach**
  - Combine the natural ability of certain viruses to cause immunogenic cell death, induce inflammatory responses and trigger immune cell infiltration into treated tumors
  - Can be combined with other therapeutic modalities (e.g. chemotherapy, checkpoint inhibitors and CAR-T cells)
- **OVs have Typically been Limited to Intratumoral Injection**
  - Metastases are not addressed by localized intratumoral injection
  - Certain tumors are difficult to directly inject safely and repeatedly (e.g. lung, pancreatic)
- **VCN is Addressing Key Challenges to Systemic OV Therapy**
  - Improving manufacturing yields to enable higher systemic doses
  - Avoiding OV off-target effects and toxicities
  - Overcoming the poorly penetrable, antiviral and immunosuppressive tumor stroma

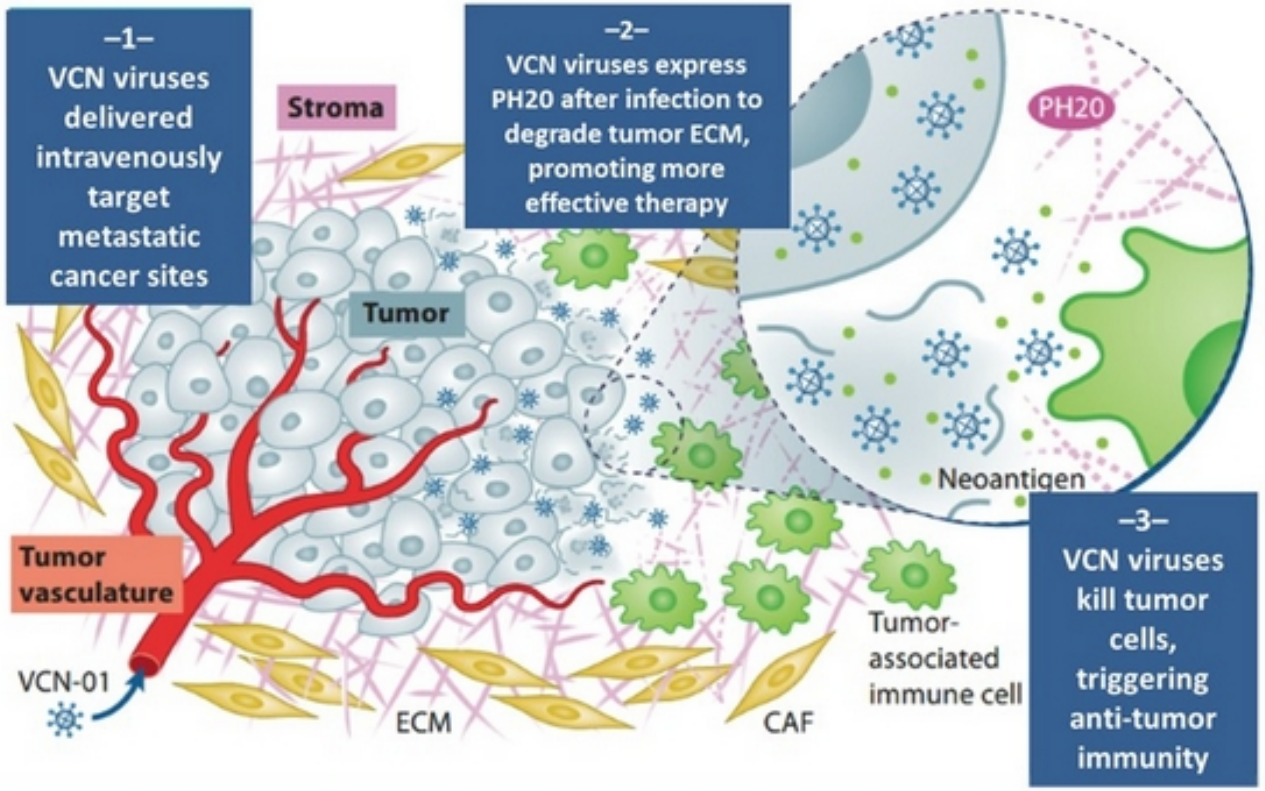
VCN-01 Oncolytic Adenovirus

- **SYSTEMIC**
  - Highly replicating
  - Decreased liver tropism
  - Treatment of primary and metastatic lesions
- **SELECTIVE**
  - Increased tumor penetration
  - Only replicates in tumors (defective Rb-E2F pathway)[1]
  - Transgene only expressed after virus replication - provides a built-in biomarker[2]
- **STROMA DEGRADING**
  - Degrades hyaluronic acid in the stroma (**PH20**)[3]
  - Increases dissemination of virus and co-administered therapeutics within the tumor
  - Increases tumor immunogenicity and immune cell infiltration



[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.
IMAGE CREDIT: https://microbewiki.kenyon.edu/index.php/Adenovirus-based_Gene_Therapy:_a_Promising_Novel_Cancer_Therapy

Unique Mechanism of Action for VCN Products



VCN-01 Clinical Trials

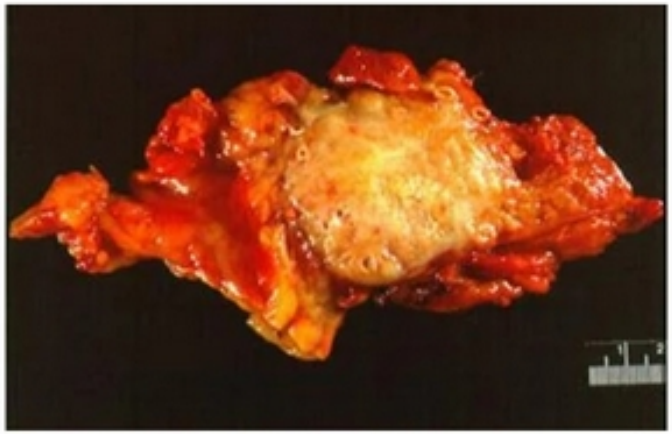
Location	Phase	Indication	Co-therapy	Route (n)	Status	NCT or EudraCT
Multicenter (ESP)	1	Part I: Solid tumor Part II: PDAC Part III: PDAC	Part I: None Parts II,III: Gemcitabine + nab-Paclitaxel	Part I: IV (16) Part II: IV (12) Part III: IV (14)	Complete[1]	NCT02045602
Multicenter (ESP)	1	PDAC	Gemcitabine + nab-Paclitaxel	IT (8)	Complete[2]	NCT02045589
Hospital Sant Joan de Déu, Barcelona	1	Retinoblastoma	None	IVit (4)	On-going partial data	NCT03284268
Institut Català d'Oncologia (ICO)	1	HNSCC	Durvalumab	IV (16)	On-going data not yet available	NCT03799744
U. Leeds	1	Adult brain tumors	None	IV (12)	IND open, trial initiating	2020-003405-59
U. Pennsylvania	1	PDAC, Ovarian	huCART-meso[3]	IV (12)	IND open, trial initiating	NCT05057715
U. Navarra	1	Pediatric brain tumors	None	IC (9-18)	Pre-IND	2020-002860-30

VCN is collaborating with world-leading clinical research institutions, 70 patients treated to date

[1]**Manuscript submitted**; data presented in part at ESMO 2019 Garcia-Carbonero (2019) *Ann Oncol* **30(S5):**v271. Link to full ESMO 2019 poster provided on Appendix Slide 31. [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. **IC** intracranial. **IV** intravenous. **IT** intratumoral. **IVit** intravitreal.

Pancreatic Ductal Adenocarcinoma (PDAC)

- PDAC accounts for 3rd highest cause of cancer-associated deaths in US (4th in EU)[1-3]
  - North America ~63,000 new cases and 53,000 deaths each year
  - Western Europe ~46,000 new cases and 43,000 deaths each year
- PDAC has the lowest survival rate of all major organ cancers
  - Median survival 4-6 months from diagnosis, 1-year survival 24%
- Treatment options for metastatic PDAC are limited[3]
  - First-line therapies include (m)FOLFIRINOX, gemcitabine + nab-paclitaxel
  - Checkpoint inhibitors have been largely ineffective
- PDAC **stroma** is a physical and immunosuppressive barrier to therapy
  - Stromal **hyaluronan** accumulation is associated with low immune response and poor prognosis[4]



Pancreatic adenocarcinoma resected from the pancreas body and tail

[1]Bengtsson (2020) *Sci Rep* **10:**16425. [2]Carioli (2021) *Ann Oncol* **32:**478. [3]For additional details and references see Appendix. [4]Tahkola (2021) *Sci Rep* **11:**12216. **(m)FOLFIRINOX** (modified) leucovorin + 5-FU + irinotecan + oxaliplatin. **nab-Paclitaxel** nanoparticle albumin-bound paclitaxel. **IMAGE:** Dragovich T. et al. "Pancreatic Cancer: Practice Essentials". Medscape, 2021. https://emedicine.medscape.com/article/280605-overview

VCN-01 Clinical Data Encourage PDAC Phase 2

- Multicenter, open-label, dose escalation study of single IV doses of VCN-01 ± gemcitabine/Abraxane® (**G/A**)[1]
  - **ARM I** *Monotherapy* VCN-01 dose finding, primarily colorectal cancer (12)
  - **ARM II** *Concomitant* VCN-01 same day as first dose of G/A in PDAC patients (16)
  - **ARM III** *Sequential* VCN-01 7-days before first dose of G/A in PDAC patients (14)[2]
- Promising antitumor activity and appropriate safety/tolerability at RP2D
- **Sequential** regimen to be advanced to Phase 2 clinical trials

Favorable Survival with VCN-01 vs Published Standard-of-Care

VCN-01 ARM III (Sequential)	VCN-01 + G/A	Published G/A alone[3]
Overall Survival, median months (n)		
$3.3x10^{12}$ vp/patient (6)	13.1	
$1.0x10^{13}$ vp/patient (6)	20.8	
Combined (both doses) (12)	**13.5**	**8.5**
Overall Response Rate (n)		
$3.3x10^{12}$ vp/patient (6)	16.7% (1)	
$1.0x10^{13}$ vp/patient (6)	83.3% (5)	
Combined (both doses) (12)	**50% (6)**	**23%**
Survival > 12 months	**8 (75%)**	
Survival > 27 months	**3 (25%)**	

[1]NCT02045602. [2]Two incorrectly enrolled patients in the $3.3x10^{12}$ vp group were replaced and excluded from endpoint analysis but are included in the safety analysis. [3]Von Hoff (2013) NEJM **369:**1691. **G/A** administered IV on days 1, 8 and 15 of each chemotherapy cycle with cycles repeated every 28-days . **RP2D** recommended phase 2 dose. **vp** virus particles. **Manuscript submitted**; data presented in part at ESMO 2019 Garcia-Carbonero (2019) *Ann Oncol* **30(S5):**v271. Link to full ESMO 2019 poster provided on Appendix Slide 31.

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

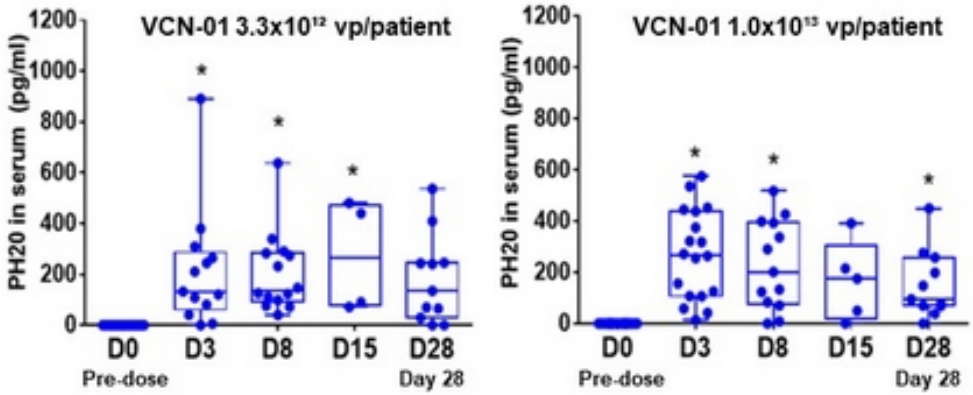
Adverse Events	Part I (Alone, n=16)		Part II (Concomitant, 12)[2]		Part III (Sequential, 14)[3]	
CTCAE Grade	Grade 1-2	Grade ≥3	Grade 1-2	Grade ≥3*	Grade 1-2	Grade ≥3
Febrile neutropenia	-	-	-	2 (16.7%)	-	-
Neutropenia/Neutrophil count decreased	2 (12.5%)	-	1 (8.3%)	1 (8.3%)	-	-
Thrombocytopenia/Platelet 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%)	-
Dyspnoea	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)

[1]NCT02045602. [2]Concomitant IV VCN-01 $3.3x10^{12}$ or $1.0x10^{13}$ vp/patient administered same day as first dose of Gemcitabine/Abraxane® (**G/A**). [3]Sequential IV VCN-01 $3.3x10^{12}$ or $1.0x10^{13}$ vp/patient administered 7-days prior to first dose of G/A. **Manuscript submitted**; data presented in part at ESMO 2019 Garcia-Carbonero (2019) *Ann Oncol* **30(S5)**:v271. Link to full ESMO 2019 poster provided on Appendix Slide 31.

VCN-01 Remodels the PDAC Tumor Matrix

Figure 1: Serum PH20 levels in patients treated with IV VCN-01 (Parts I-III)



Built-in biomarker: hyaluronidase (PH20) levels in patient sera are linked to viral replication and demonstrate sustained VCN-01 activity in tumors (Figure 1)

Turns cold tumors "hot": VCN-01 remodels the tumor matrix and the immunological environment and promotes tumor inflammation (Figure 2)

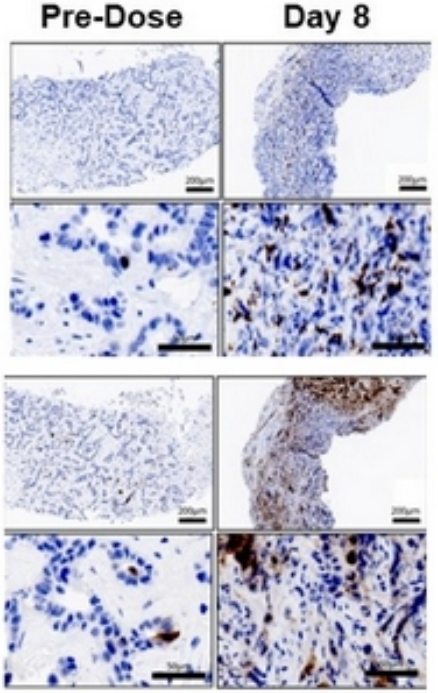
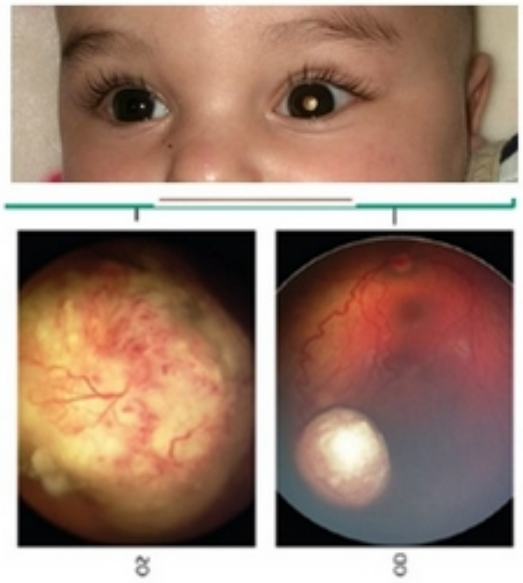


Figure 2: IHC of biopsies from hepatic metastases of a PDAC patient treated with IV VCN-01

IHC immunohistochemical staining IDO indoleamine 2,3-dioxygenase. **Manuscript submitted**; data presented in part at ESMO 2019 Garcia-Carbonero (2019) *Ann Oncol* **30(S5)**:v271. Link to full ESMO 2019 poster provided on Appendix Slide 31.

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



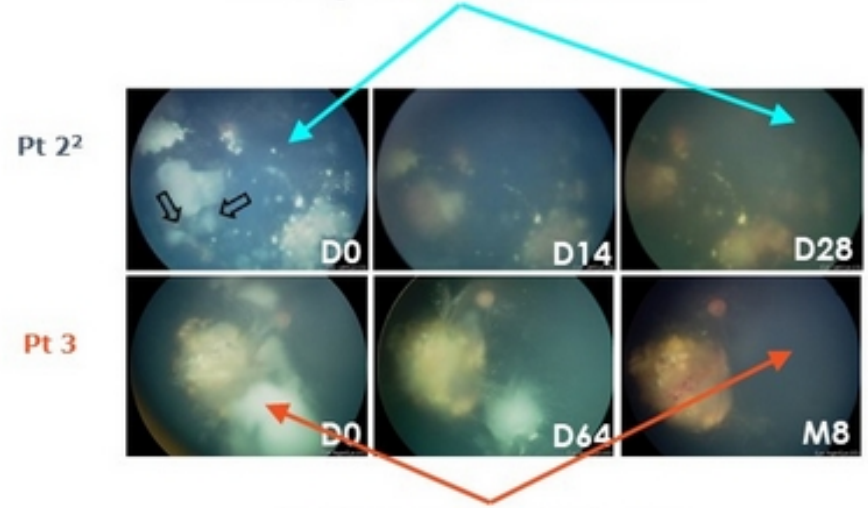
[1]https://www.cancer.org/cancer/retinoblastoma/about/key-statistics.html. [2]Stacey (2021) *Ophthalmology* **128**:1369. [3]One Retinoblastoma World Map https://map.1rbw.org/. [4]For additional details and references see Appendix. **IMAGE:** Courtesy of Hospital Sant Joan de Déu, Barcelona

VCN-01 in Retinoblastoma

- Single center, open-label dose escalation study of intravitreal (**IVT**) VCN-01[1-3]
  - Children aged 1-12 years (n=4 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=3) on days 1 and 15
- Promising antitumor activity and appropriate safety/tolerability at RP2D
  - Enucleation **avoided** in 1 of 4 patients
  - 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 with High Dose VCN-01

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



Complete tumor regression[3]

[1]EudraCT 2016-001060-11. 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 on Appendix Slide 31. **RP2D** recommended phase 2 dose. **vp** virus particles.

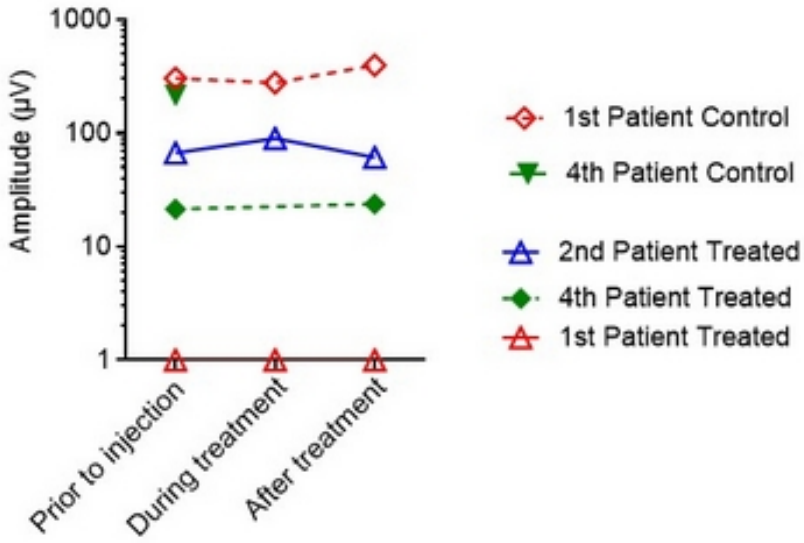
Interim Safety Data for Intravitreal VCN-01

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)

Stable Electroretinographic Signals



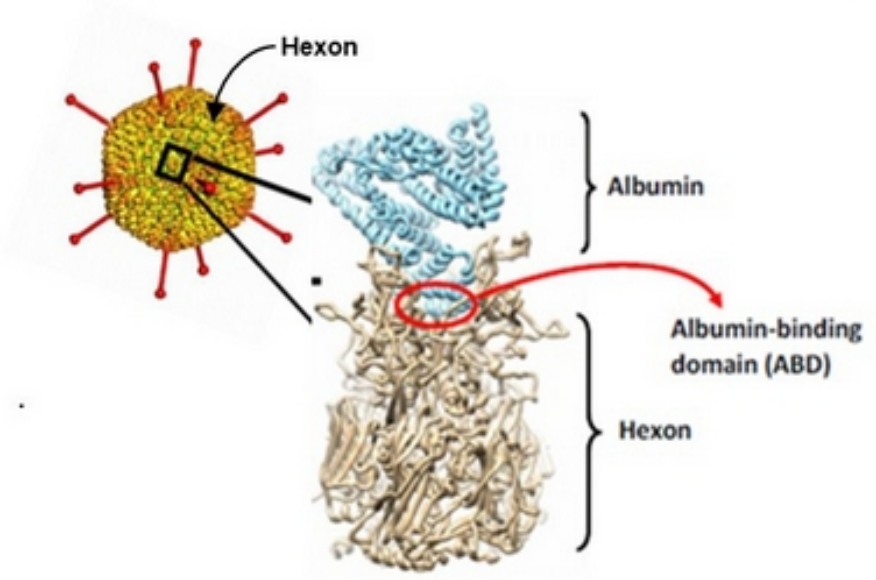
[1]NCT03284268. [2]Intravitreal VCN-01 doses of $2.0x10^9$ virus particles (**vp**) per eye (Patient 1) or $2.0x10^{10}$ vp per eye (Patients 2-4) administered on days 1 and 15. Data presented at International Oncolytic Virus Conference IOVC2021, 07 November 2021, Sedona, AZ. Link to IOVC2021 slide deck provided on Appendix Slide 31.

VCN-01 Next Steps

- **PDAC Phase 2 Clinical Trial**
  - Finalizing protocol for a multinational, multicenter, study evaluating IV VCN-01 with gemcitabine/nab-paclitaxel compared to gemcitabine/nab-paclitaxel alone
  - Newly-diagnosed metastatic PDAC patients treated with gemcitabine/nab-paclitaxel first line therapy
  - Principal Investigator **Dr. Manuel Hidalgo Medina, MD PhD**
    - Chief of the Division of Hematology and Medical Oncology at Weill Cornell Medicine/New York-Presbyterian Hospital
    - Member of the Board of Directors, Bristol Myers Squibb
- **Rb Phase 2/3 Pivotal Trial**
  - Developing a protocol for a multinational, multicenter, study evaluating intravitreal VCN-01
  - Principal Investigator: **Dr. Guillermo Chantada, MD PhD**
    - Principal Researcher, Associate Physician, Hospital Sant Joan de Déu, Barcelona, Spain; National Council of Research in Argentina (CONICET); Scientific Director, Pediatric Hemato-Oncology Service of the Hospital Universitario Austral, Argentina and Hospital Pereira Rossell, Montevideo, Uruguay
    - President, International Society of Paediatric Oncology

Albumin Shield™ to Expand the VCN Platform

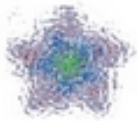
- VCN has developed the Albumin Shield technology to protect OVs as they travel to the tumors[1,2]
- Albumin Shield modified OVs are coated by albumin and protected from circulating antibodies in cancer patients pre-exposed to adenovirus
- Albumin Shield may enable **multiple intravenous administrations** for hard-to-treat patients
- Albumin Shield first candidate **VCN-11** is being prepared for a Phase 1 clinical trial in ovarian cancer and other solid tumors



Albumin Shield modified OVs express an albumin binding domain (ABD) on the virus surface (hexon) that binds host serum albumin. The modification allows parent and the progeny to be albumin coated for continued protection

[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.

VCN Albumin Shield Platform Candidates

COMMON FEATURES		PRODUCT SPECIFIC FEATURES
CLINICALLY-TESTED ADENOVIRUS EXPRESSING PH20 HYALURONIDASE TO DEGRADE STROMA		VCN-11: Hyaluronidase alone
+		
ALBUMIN SHIELD™ TO PREVENT NEUTRALIZATION BY CIRCULATING ANTI-VIRAL ANTIBODIES TO FACILITATE IV MULTIDOSING		Hyaluronidase + Bispecific Engagers
+		
UNIQUE MULTIFUNCTIONAL PROTEINS TO TURN COLD TUMORS HOT		Hyaluronidase + Immunomodulators

Albumin Shield platform invites potential licensing opportunities

VCN Potential Competitive Advantages

- **VCN OVs ARE OPTIMIZED FOR SYSTEMIC DELIVERY**
  - Opportunity for virus to pursue metastatic lesions in addition to primary tumors
  - Selectivity has the potential to improve safety and pharmacokinetics (liver sequestration ↓ tumor penetration ↑)
- **VCN OVs ARE HIGHLY REPLICATIVE**
  - Fulfilling systemic dosing requirements
  - Potent transgene expression is a built-in biomarker for tracking viral replication in the tumor
- **VCN OVs EXPRESS HYALURONIDASE to DEGRADE TUMOR STROMA**
  - Increased tumor dissemination allowing co-administered chemotherapies and immunotherapies (CAR-T, CPI)
  - Improved infiltration of anti-tumor immune responders to improve efficacy
- **VCN OVs ENABLE MULTIDOSING in HARD-TO-TREAT TUMORS**
  - Preclinically validated platform with decreased NAb susceptibility for systemic re-administration
  - Co-delivery of hyaluronidase and additional therapeutic transgenes

CAR-T chimeric antigen receptor T-cell. **CPI** checkpoint inhibitor. **NAb** neutralizing antibody. **Rb-E2F** pathway reviewed in Giacinti (2006) *Oncogene* **25**:5220 and Polager (2009) *Nat Rev Cancer* **9**:738.

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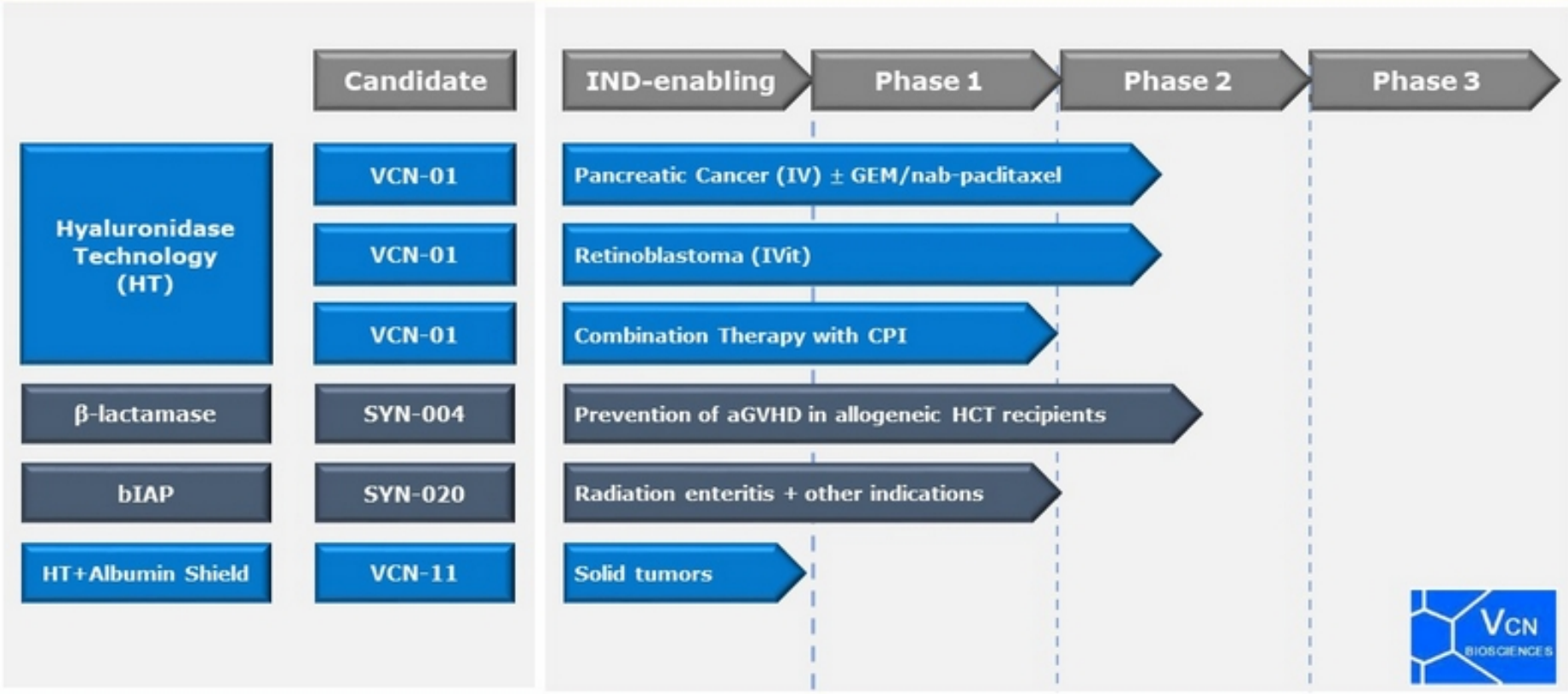
Pipeline and Milestones

SYN and VCN Pro Forma Combined Pipeline After Acquisition



aGVHD acute graft-vs-host disease; **allogeneic HCT** allogeneic hematopoietic cell transplant. **bIAP** bovine intestinal alkaline phosphatase. **CPI** immune checkpoint inhibitor. **GEM/nab+paclitaxel** Gemcitabine + Abraxane®. **IT** intratumoral. **IV** intravenous. **IVit** intravitreal.

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Upcoming News and Potential Milestones After Acquisition

Q1 2022	Q2 2022	Q3 2022	Q4 2022	H1 2023
• SYN+VCN merger closing • VCN-01 U. Leeds ISS first patient dosed • VCN-01 UPenn ISS first patient dosed	• SYN-020 Phase 1 MAD topline data • SYN-004 Phase 1b/2a data 1st antibiotic cohort	• SYN-020 Phase 2a initiation (indication TBD) • SYN-004 Phase 1b/2a 2nd cohort begins dosing	• Initiation of VCN-01 PDAC Phase 2	• SYN-020 Phase 2a data (indication TBD) • SYN-004 Phase 1b/2a data 2nd antibiotic cohort • VCN-01 RB proposed pivotal trial initiation • VCN-11 IND Filing

SYN-VCN: Accelerating the Pathway to Value

- **Advanced Clinical Oncology Pipeline and Platform**
  - Multiple SYN and VCN clinical assets
  - Lead orphan cancer indications with critical unmet medical need
  - Continued expansion of the pipeline with joint discovery programs
- **Synergies Between Teams**
  - Complementary skill sets and experience in OVs, gene therapy, CMC, and product development
  - Immediate access to laboratory facilities and personnel for joint discovery and development
  - Shared international clinical trial expertise
- **Multinational Presence**
  - Facilitates access to clinical study sites, patients, regulatory agencies
  - Establishes a footprint in key EU market for partnering and commercialization
  - Access to US financial markets

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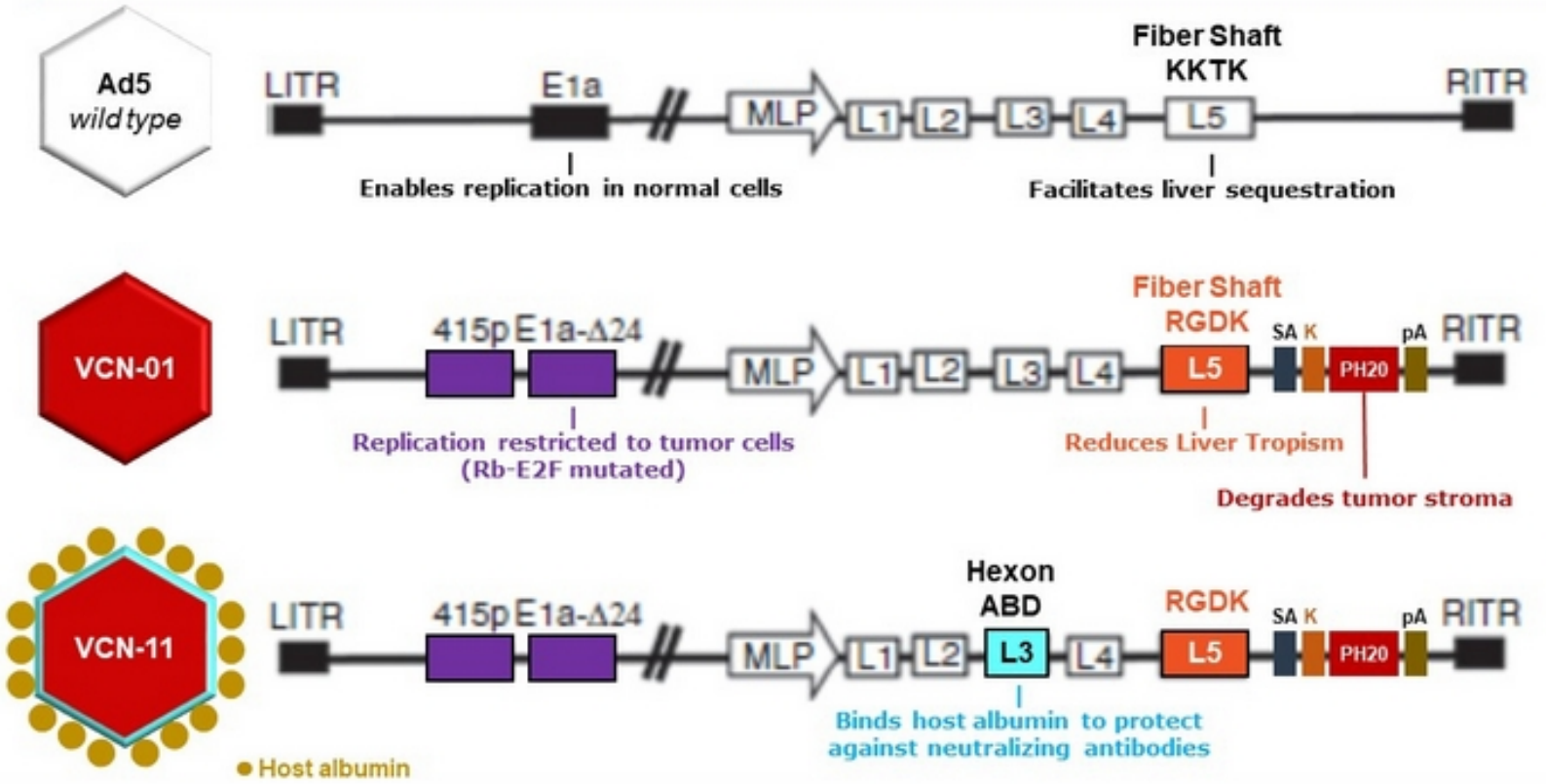
Appendix

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**)

IV VCN-01 Clinical Trial Population (Multicenter ESP[1])

Characteristics	Part I (VCN-01 Alone)				Part II (Concomitant)[2]		Part III (Sequential)[3]	
Dose, vp/patient	**$1.0x10^{11}$**	**$1.0x10^{12}$**	**$3.3x10^{12}$**	**$1.0x10^{13}$**	**$3.3x10^{12}$**	**$1.0x10^{13}$**	**$3.3x10^{12}$**	**$1.0x10^{13}$**
No Patients, n	3	4	3	6	6	6	8*	6
Median Age, years	67	70	72	54	61	59	62	63
Male / Female	2 / 1	3 / 1	2 / 1	5 / 1	3 / 3	4 / 2	1 / 7	2 / 4
ECOG Status								
0	1	2	1	1	2	2	4	2
1	2	2	2	5	4	4	4	4
Primary Disease								
Colorectal Cancer (IV)	3	4	3	5	-	-	-	-
Head and Neck	-	-	-	1	-	-	-	-
Pancreatic (III)	-	-	-	-	1	1	2	-
Pancreatic (IV)	-	-	-	-	5	5	6	6
Site of Metastasis								
Liver ± other organ	2	2	1	6	5	5	5	6
Other	1	2	2	-	-	-	1	-

*Two incorrectly enrolled patients were replaced and excluded from endpoint analysis but are included in the safety analysis (ESMO 2019)

[1]NCT02045602. [2]Concomitant VCN-01 administered same day as first dose of Gemcitabine/Abraxane® (**G/A**). [3]Sequential VCN-01 administered 7-days prior to first dose of G/A. **Manuscript submitted**; data presented in part at ESMO 2019 Garcia-Carbonero (2019) *Ann Oncol* **30(S5)**:v271. Link to full ESMO 2019 poster provided on Appendix Slide 31.

Concomitant IV VCN-01 & G/A in PDAC (Multicenter ESP[1])

Part II: All AEs Regardless of Relatedness to VCN-01 (ESMO 2019)[1]

Adverse Reaction	Pts	All Grades		Grade ≥3		Adverse Reaction	All Grades		Grade ≥3	
Preferred Term	N	n	%	n	%	*Preferred Term*	n	%	n	%
Pyrexia	12	8	66.7%	0	0.0%	Bacteremia	1	8.3%	1	8.3%
Thrombocytopenia	12	7	58.3%	4	33.3%	Enterocolitis*	1	8.3%	1	8.3%
Asthenia	12	6	50.0%	1	8.3%	Hepatitis, acute	1	8.3%	1	8.3%
Musculoskeletal pain	12	4	33.3%	0	0.0%	Chills	1	8.3%	0	0.0%
Neutropenia	12	3	25.0%	2	16.7%	Diarrhea	1	8.3%	0	0.0%
Decreased appetite	12	3	25.0%	0	0.0%	Dizziness	1	8.3%	0	0.0%
Nausea	12	3	25.0%	0	0.0%	Headache	1	8.3%	0	0.0%
Febrile neutropenia	12	2	16.7%	2	16.7%	Hypotension	1	8.3%	0	0.0%
Transaminase increase	12	2	16.7%	1	8.3%	Myalgia	1	8.3%	0	0.0%
Vomiting	12	2	16.7%	0	0.0%	Productive cough	1	8.3%	0	0.0%

Combined data for $3.3x10^{12}$ and $1.0x10^{13}$ vp/patient VCN-01 IV doses administered on the **same day** as the first dose of G/A.
Two DLTs at $1x10^{13}$ vp/patient dose: one patient suffered febrile neutropenia (Grade 4); a second patient died from combined acute hepatitis + thrombocytopenia + enterocolitis (Grade 5)*

[1]NCT02045602. **G/A** Gemcitabine/Abraxane® (nab-paclitaxel). **PDAC** pancreatic ductal adenocarcinoma. **vp** virus particle. **Manuscript submitted**; data presented in part at ESMO 2019 Garcia-Carbonero (2019) *Ann Oncol* **30(S5)**:v271. Link to full ESMO 2019 poster provided on Appendix Slide 31.

Sequential IV VCN-01 then G/A in PDAC (Multicenter ESP[1])

Part III: All AEs Regardless of Relatedness to VCN-01 (ESMO 2019)[1]

Adverse Reaction	Pts	All Grades		Grade ≥3		Adverse Reaction	All Grades		Grade ≥3	
Preferred Term	N	n	%	n	%	*Preferred Term*	n	%	n	%
Pyrexia	14	9	64.3%	0	0.0%	Anaemia	2	14.3%	0	0.0%
Nausea	14	4	28.6%	0	0.0%	Neutropenia	1	7.1%	0	0.0%
Vomiting	14	3	21.4%	0	0.0%	Thrombocytopenia	1	7.1%	0	0.0%
Influenza-like Illness	14	3	21.4%	0	0.0%	Cough	1	7.1%	0	0.0%
Diarrhea	14	2	14.3%	1	7.1%	Headache	1	7.1%	0	0.0%
Asthenia	14	2	14.3%	0	0.0%	Herpes Simplex	1	7.1%	0	0.0%
Transaminase increase	14	2	14.3%	0	0.0%	Rhinorrhoea	1	7.1%	0	0.0%
ALT increase	14	1	7.1%	1	7.1%					
AST increase	14	1	7.1%	1	7.1%					

Combined data for $3.3x10^{12}$ and $1.0x10^{13}$ vp/patient VCN-01 IV doses administered **7-days prior** to first dose of G/A.
One AE of diarrhea (Grade 3) at the $1x10^{13}$ vp/patient dose was incorrectly reported as a DLT but subsequently reclassified.

[1]NCT02045602. **DLT** dose limiting toxicity. **G/A** Gemcitabine/Abraxane® (nab-paclitaxel). **PDAC** pancreatic ductal adenocarcinoma. **Manuscript submitted**; data presented in part at ESMO 2019 Garcia-Carbonero (2019) *Ann Oncol* **30(S5)**:v271. Link to full ESMO 2019 poster provided on Appendix Slide 31.

Intratumoral VCN-01 In PDAC (Multicenter ESP[1])

- Multicenter, open-label, dose escalation study of intratumoral (**IT**) VCN-01 with IV chemotherapy[2]
  - **Level I** VCN-01 1×10^{10} vp on days 1, 22, 43 and gemcitabine (**G**) on days 1, 8, 15, 22, 29, 35, 43 (n=2)
  - **Level II** VCN-01 1×10^{11} vp on days 1, 29, 57 and gemcitabine/Abraxane® (**G/A**) on days 1,8, 15 and then every 4 weeks (n=6)
- VCN-01 replicated in tumors, expressed the PH20 transgene, and reduced tumor stiffness in evaluated patients
  - Detailed study results published[2]
- VCN-01 IT administration is not currently being pursued
  - IV administration preferred

Adverse Events	Treatment Related AEs (8)	
CTCAE Grade	Grade 1-2	Grade ≥3*
Anemia	1 (12.5%)	-
Leukopenia	-	1 (12.5%)
Neutropenia	2 (25.0%)	-
Thrombocytopenia	2 (25.0%)	-
Constipation	2 (25.0%)	-
Dyspepsia	1 (12.5%)	-
Melena	1 (12.5%)	-
Nausea	2 (25.0%)	-
Vomiting	1 (12.5%)	-
Asthenia/Fatigue	**5 (62.5.0%)**	**1 (12.5%)**
Pyrexia	**4 (50.0%)**	-
Transaminase increased	1 (12.5%)	2 (25.0%)
GGT increased	1 (12.5%)	-
Decreased appetite/Anorexia	2 (25.0%)	-
Hypophosphatemia	-	1 (12.5%)
Arthralgia / Musculoskeletal Pain	2 (12.5%)	-
Dysgeusia	1 (12.5%)	-
Epistaxis	1 (12.5%)	-

*One patient at the $1x10^{11}$ vp dose died from localized abdominal fluid collection associated with gastric necrotic ulcer and upper GI bleeding (grade 5)

[1]NCT02045589. [2]Bazan-Peregrino (2021) *J Immunother Cancer* **9**:e003254. **Abraxane®** nab-paclitaxel.

Intratumoral VCN-01 in PDAC (Multicenter ESP[1])

All AEs Regardless of Relatedness to VCN-01 (ESMO 2019)[1]

Adverse Reaction	Pts	All Grades		Grade ≥3		Adverse Reaction	All Grades		Grade ≥3	
Preferred Term	N	n	%	n	%	*Preferred Term*	n	%	n	%
Asthenia/Fatigue	8	6	75.0%	1	12.5%	Localized intraabdom. fluid collection	1	12.5%	1*	12.5%
Pyrexia	8	4	50.0%	0	0.0%	Febrile Neutropenia	1	12.5%	1	12.5%
Hypertransaminemia	8	3	37.5%	2	25.0%	Hypophosphatemia	1	12.5%	1	12.5%
Neutropenia	8	3	37.5%	1	12.5%	Anemia	1	12.5%	0	0.0%
Thrombocytopenia	8	2	25.0%	0	0.0%	Leucopenia	1	12.5%	0	0.0%
Anorexia	8	2	25.0%	0	0.0%	GGT increased	1	12.5%	0	0.0%
Arthromyalgia	8	2	25.0%	0	0.0%	Diarrhea	1	12.5%	0	0.0%
Neurotoxicity	8	2	25.0%	0	0.0%	Nausea	1	12.5%	0	0.0%
Constipation	8	2	25.0%	0	0.0%	Vomiting	1	12.5%	0	0.0%
						Epistaxis	1	12.5%	0	0.0%

Combined data for VCN-01 $1.0x10^{10}$ vp/dose IT x 3 + IV Gemcitabine (**G**; n=2) and VCN-01 $1.0x10^{11}$ vp/dose x 3 + IV Gemcitabine/ Abraxane® (**G/A**; n=6). Two DLTs observed at $1x10^{11}$ vp/patient dose: two patients had transaminase increases (Grade 3-4); a third patient died from intraabdominal fluid collection associated with gastric necrotic ulcer and upper GI bleeding (Grade 5)*

[1]NCT02045589. **DLT** dose limiting toxicity. **G/A** Gemcitabine/Abraxane® (nab-paclitaxel). **PDAC** pancreatic ductal adenocarcinoma. **Manuscript submitted**; data presented in part at ESMO 2019 Garcia-Carbonero (2019) *Ann Oncol* **30(S5):**v271. data presented at ESMO 2019 Hidalgo (2019) Ann Oncol 30(S5):v171. Link to full ESMO 2019 poster provided on Appendix Slide 31.

VCN Biosciences Key Publications

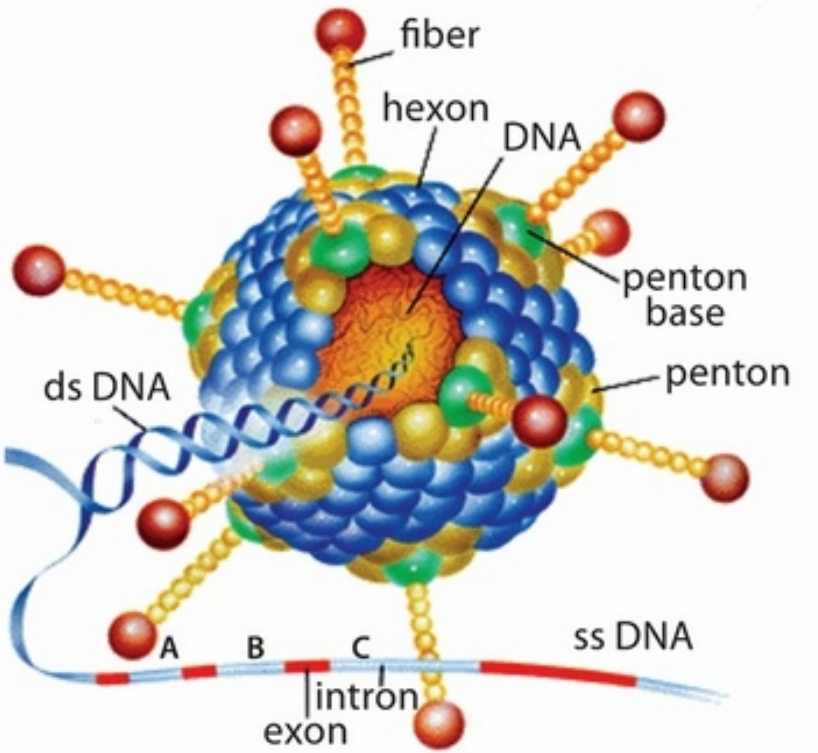
- Bayo-Puxan N et al. (2006) Role of the putative heparan sulfate glycosaminoglycan-binding site of the adenovirus type 5 fiber shaft on liver detargeting and knob-mediated retargeting. *J Gen Virol* **87:**2487–2495
- Rojas J et al. (2012) Improved systemic antitumor therapy with oncolytic adenoviruses by replacing the fiber shaft HSG-binding domain with RGD. *Gene Ther* **19:**453–457
- 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
- 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
- Martínez-Vélez N et al. (2019) The oncolytic adenovirus VCN-01 as therapeutic approach against pediatric osteosarcoma. *Clin Cancer Res* **22:**2217-25
- Bazan-Peregrino M et al. (2021) VCN-01 disrupts pancreatic cancer stroma and exerts antitumor effects. *J ImmunoTher Cancer* **9:**e003254.
- Rojas LA et al. (2016) Albumin-binding adenoviruses circumvent pre-existing neutralizing antibodies upon systemic delivery. *J Control Rel* **237:**78–88
- Mato-Berciano A et al. (2021) Oncolytic adenovirus with hyaluronidase activity that evades neutralizing antibodies: VCN-11. *J Control Rel* **332:**517-528
- 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 **Poster** available at: http://www.vcnbiosciences.com/images/pdfs/ESMO2019%20Poster%20MoA%20VCN-01%20vFinal.pdf
- Garcia-Carbonero 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. **Poster** available at: http://www.vcnbiosciences.com/images/pdfs/ESMO%202019%20Poster%20VCN-01%20IV%20vFinal.pdf
- 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. **Slides** available at: http://www.vcnbiosciences.com/images/pdfs/Retinoblastoma_IOVC_2021v1.pdf

Oncolytic Viruses

- Oncolytic viruses (**OVs**) infect and lyse cancer cells without harming normal cells
  - Can be naturally occurring or genetically engineered to improve selectivity, safety and efficacy
  - Can be developed from multiple virus types, including **adenovirus**, herpes simplex (HSV), measles, parvovirus, reovirus, and vaccinia
- OV tumor cell lysis can reverse immune tolerance to tumors
  - Exposes tumor-specific and tumor-associated antigens (turning "cold" tumors "hot")
  - Retarget the adaptive immune system to induce a long-lasting anti-tumor response
- OVs face multiple challenges to systemic delivery
  - Poorly penetrable, antiviral and immunosuppressive **tumor stroma**
  - Host anti-OV immune responses
  - Sequestration of OV in the spleen and liver[1]

Reviewed in: Balachandran (2019) *Gastroenterology* **156:**2056. Gonzalez-Pastor (2021) *Cancer Gene Ther* **28:**375. Hemminki (2020) *J Hematol Oncol* **13:**84. Martinez-Quintanilla (2019) *J Clin Invest* **129:**1407. Ungerechts (2016) *Mol Ther Methods Clin Dev* **3:**16018. Can be associated with liver toxicity and increases in liver enzymes.

Adenovirus Overview



- Adenoviruses (**AdV**) are medium-sized (90–100 nm), non-enveloped viruses with icosahedral shaped capsids containing a double-stranded DNA (**dsDNA**) genome typically 30-36 kb in length[1-3]
- There are at least 57 AdV serotypes classified into 7 subgroups (A to G)[2]
- AdV2 and AdV5 (Group C) are the most commonly-used viruses for OV design[1-4]
  - Large packaging capacity[5]
  - Infect both dividing and non-dividing cells
  - Lack of integration into the host genome
  - Mild nature of illness after infection

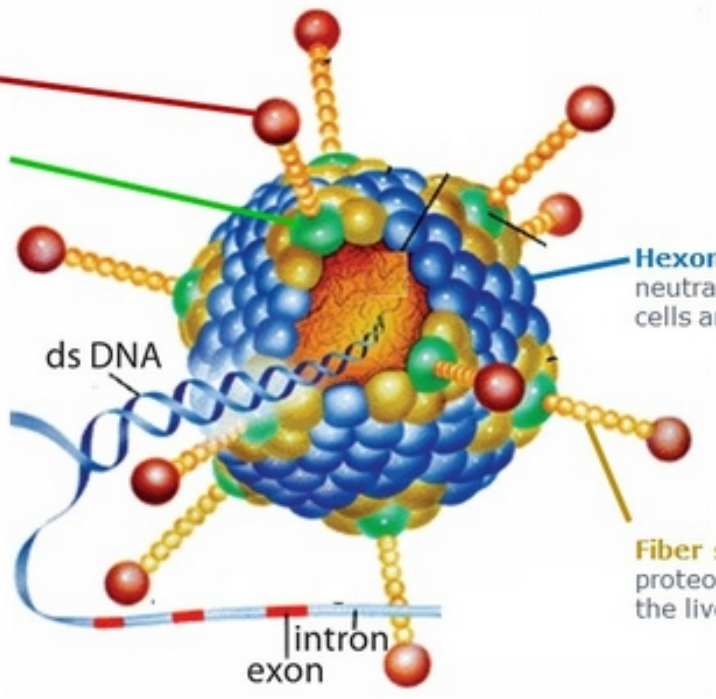
[1]Charman (2019) *FEBS Lett* **593:**3531. [2]Hemminki (2020) *J Hematol Oncol* **13:**84. [3]Hajeri (2020) *Cancers* **12:**1504. [4]Gonzalez-Pastor (2021) *Cancer Gene Ther* **28:**375–89. [5]Recombinant Ad5 genomes can be up to 105% of the 36 kb genome of the native Ad5.
IMAGE: https://microbewiki.kenyon.edu/index.php/Adenovirus-based_Gene_Therapy:_a_Promising_Novel_Cancer_Therapy

Oncolytic Adenoviruses

Structural features determining virus viability, tumor access and efficacy[1-4]

Virus attaches to target cell by interaction between the **fiber knob** and the host cell coxsackievirus and adenovirus receptor (**CAR**)

Virus internalized into target cell by interaction between the **penton base** and target cell αvβ3 and αvβ5 integrins



Hexon components can interact with host neutralizing antibodies, receptors, proteins, and cells and elicit an AdV-specific T-cell response

Genetic engineering can confer tumor selectivity and improve therapeutic efficacy[2,3]

- Conditionally replicate only in tumor cells
- Express therapeutic payloads that elicit or enhance anti-tumor effects
- Avoid host and tumor defense mechanisms

Fiber shaft can bind to heparan sulphate proteoglycans (**HSPG**) and facilitate uptake into the liver[4]

[1]Hajeri (2020) *Cancers* **12:**1504. [2]Gonzalez-Pastor (2021) *Cancer Gene Ther* **28:**375. [3]Yamamoto (2017) *Cancer Sci* **108:**831. [4]Khare (2012) *J Virol* **86:**2293, as much as 95-98% of an IV dose of unmodified Ad5 is trafficked to the liver where ~90% of the dose is sequestered and destroyed by resident liver macrophages called Kupffer cells. **IMAGE:** https://microbewiki.kenyon.edu/index.php/Adenovirus-based_Gene_Therapy:_a_Promising_Novel_Cancer_Therapy

Pancreatic Cancer Cases and Deaths 2020[1]

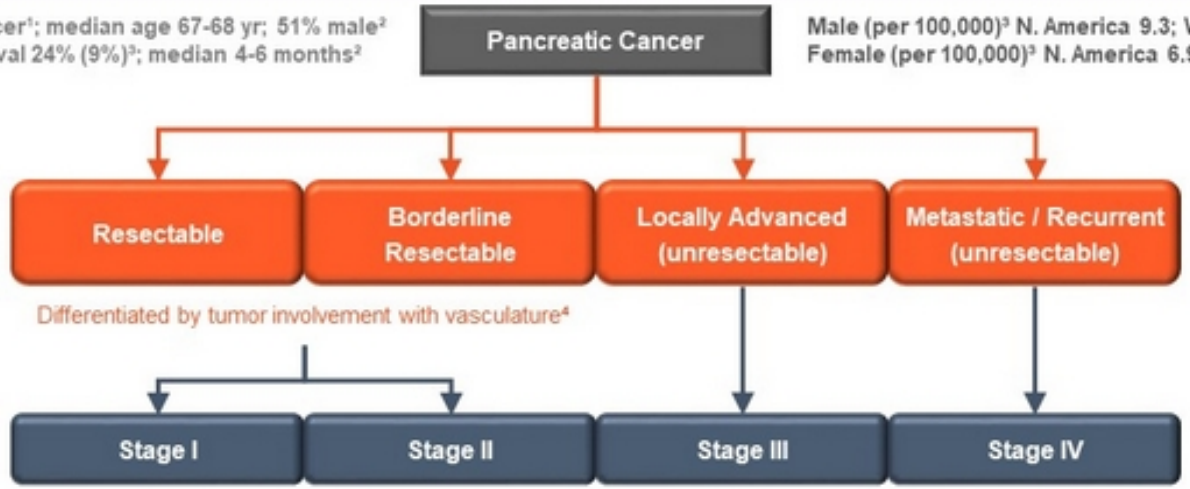
REGION	ALL		Male			Female		
	New Cases	Deaths	New Cases	No. per 100,000	Deaths	New Cases	No. per 100,000	Deaths
Caribbean	2,746	2,668	1,479	5.1	1,440	1,267	3.6	1,228
Central America	6,576	6,244	3,232	3.8	3,111	3,344	3.2	3,133
South America	28,030	27,118	13,766	5.4	13,346	14,264	4.3	13,772
Northern America	62,643	53,277	32,938	9.3	27,888	29,705	6.9	25,389
Eastern Asia	181,450	173,212	98,421	7.0	93,135	83,029	4.8	80,077
South-Eastern Asia	16,485	16,167	9,458	2.9	9,309	7,027	1.8	6,858
South-Central Asia	21,954	21,144	13,634	1.5	13,089	8,320	0.9	8,055
Western Asia	13,812	13,511	7,975	7.1	7,804	5,837	4.4	5,707
Central & Eastern Europe	44,371	42,788	22,576	9.9	21,812	21,795	5.6	20,976
Western Europe	45,461	43,336	22,672	9.9	21,684	22,789	7.4	21,652
Southern Europe	30,836	28,517	15,250	8.4	14,409	15,586	6.2	14,108
Northern Europe	19,448	17,493	9,712	8.3	8,793	9,736	6.7	8,700
Australia and New Zealand	4,674	3,776	2,370	7.9	1,952	2,304	6.7	1,824
WORLD	**495,773**	**466,003**	**262,865**	**5.7**	**246,840**	**232,908**	**4.1**	**219,163**

[1]Data from The Global Cancer Observatory, GLOBOCAN International 2020 survey of persons 0-74 years. https://gco.iarc.fr/today/data/factsheets/cancers/13-Pancreas-fact-sheet.pdf. For additional US specific data see da Costa (2020) *JNCI Cancer Spectrum* **4**:pkaa033.

Pancreatic Cancer Staging

PDAC >90% pancreatic cancer[1]; median age 67-68 yr; 51% male[2]
1-year (5-year) overall survival 24% (9%)[3]; median 4-6 months[2]

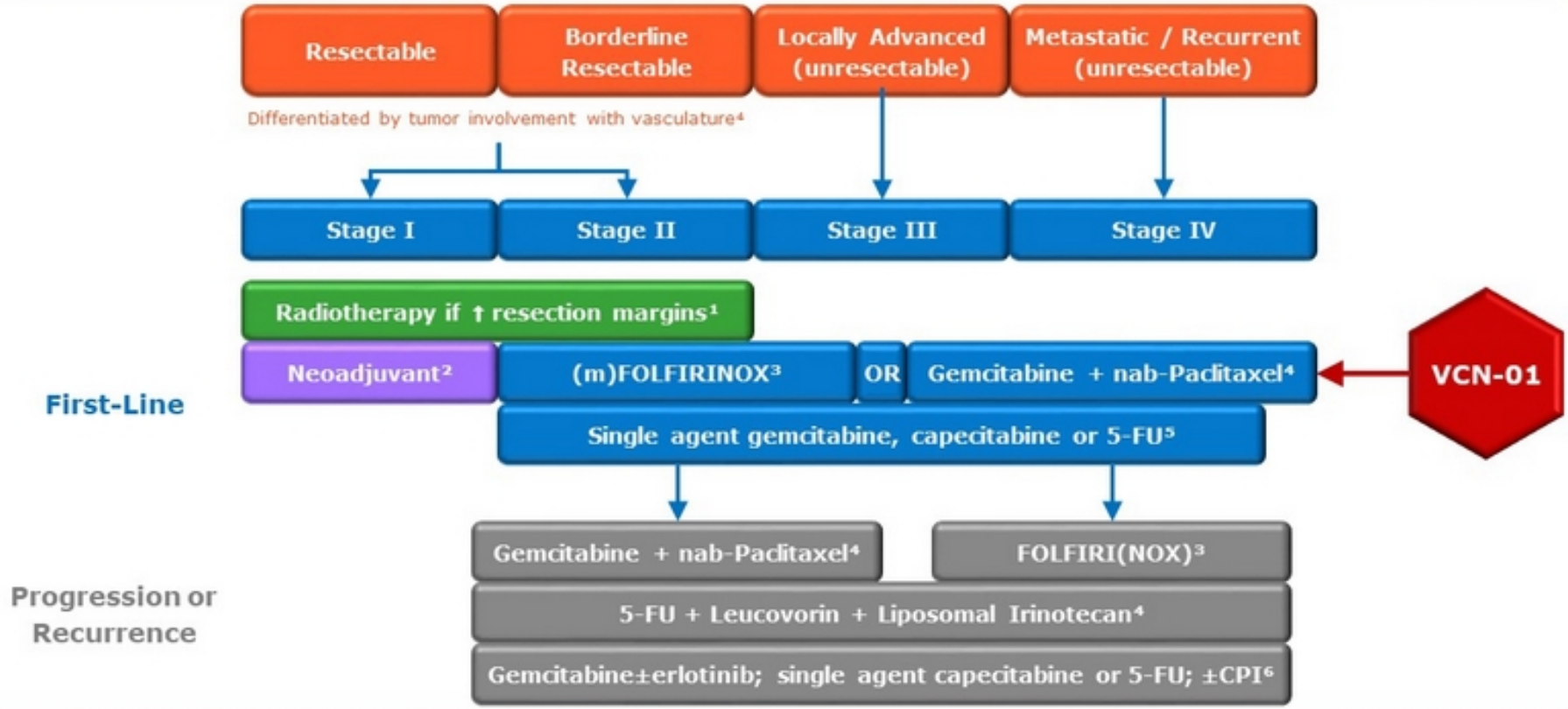
Male (per 100,000)[3] N. America 9.3; W. Europe 9.9; E. Asia 7.0
Female (per 100,000)[3] N. America 6.9; W. Europe 7.4; E. Asia 4.8



AJCC Stage	IA	IB	IIA	IIB	III	IV
T-N-M[5]	T1 N0 M0	T2 N0 M0	T3 N0 M0	T1-3 N1 M0	T1-3 N2 M0 T4 NX-2 M0	TX-4 NX-2 M1
Median Age, yr (range)[6]	66 (30-88)	66 (31-89)	68 (31-93)	66 (30-95)	67 (31-94)	67 (30-95)
Male (Female), %[6]	51 (49)	48 (52)	50 (50)	51 (49)	50 (50)	54 (46)
Proportion of PDAC, %[2]	1.3%	4.4%	11.5%	16.3%	10.6%	**56.0%**
5-Year Survival, %[2]	31.7%	11.8%	9.0%	8.7%	1.9%	**0.5%**
Pancreas Head, %[6]	61%	58%	77%	85%	75%	55%

[1]**PDAC** pancreatic ductal adenocarcinoma. Cancers in the pancreas head (~70%) are diagnosed earlier than cancers in the body or tail (each ~15%), which have a worse prognosis, Sarantis (2020) *World J Gastrointest Oncol* **12:**173-181. [2]Bengtsson (2020) *Sci Rep* **10:**16425. [3]GLOBOCAN 2020 survey of persons 0-74 years. Ushio (2021) *Diagnostics* **11:**562. [4]Toesca (2018) *Int J Radiation Oncol Biol Phys* **100:**1155-1174. [5]American Joint Committee on Cancer **T**umor size, **N**odal involvement, **M**etastasis. [6]Yu (2015) *Gut* **64:**1783-9.

Pancreatic Cancer Treatment



[1]Radiotherapy is used in <20% of PDAC cases as most present at a late stage. [2]Neoadjuvant chemotherapy - if indicated - is identical to first-line chemotherapy. [3]Patients with good performance status ECOG 0-1. [4]Patients with good to moderate performance status ECOG 0-2. [5]Patients with poor performance status ECOG 3-4. [6]Checkpoint inhibitor (**CPI** e.g. pembrolizumab) added in some cases but CPIs have had very limited efficacy in PDAC to date. **(m)FOLFIRINOX** (modified) leucovorin + 5-FU + irinotecan + oxaliplatin. **nab-Paclitaxel** nanoparticle albumin-bound paclitaxel. Tempero (2021) *J Natl Compr Canc Netw* **19**:439.

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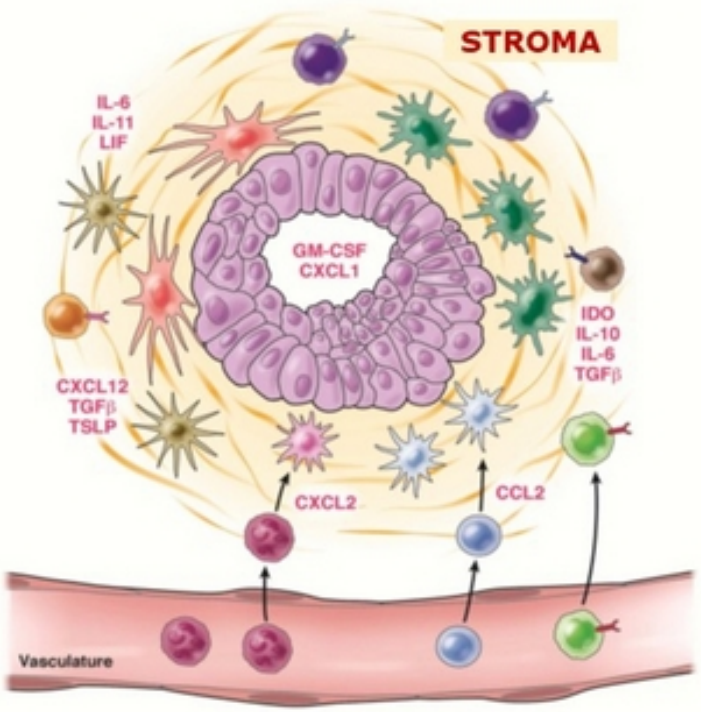
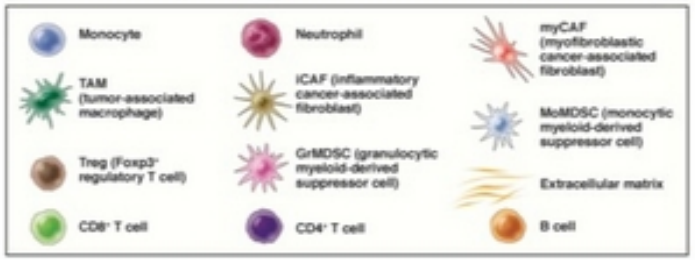
Tumor Stroma Barriers to Therapy

Pancreatic Ductal Cell Carcinoma (PDAC)



- PDAC stroma can account for 50-70% of the total tumor mass[1,2] (up to 90% of the tumor volume[3,4])
- PDAC stroma is characterized by dense **immunosuppressive** desmoplasia which stems from activated pancreatic stellate cells (**PSCs**) that produce collagens, laminin, and fibronectin[1-5]
- Extracellular matrix components such as **hyaluronic acid** can creating a physical barrier to the delivery of chemotherapy and immunotherapeutics by elevating interstitial fluid pressures and collapsing intratumoral vasculature[1-5]
- Malignant cells, fibroblasts, and myeloid cells secrete immunosuppressive cytokines and chemokines that prevent effective anti-tumor T cell responses
- PDAC has remained almost completely resistant to immunotherapy (including checkpoint inhibitors)[1,3]
- Stromal **hyaluronan** accumulation associated with low immune response and poor prognosis[6]



Graphic from [1]Balachandran (2019) *Gastroenterology* **156**:2056. [2]Sarantis (2020) *World J Gastrointest Oncol* **12**:173. [3]Orth (2019) *Radiation Oncol* **14**:141. [4]Christenson (2020) *Lancet Oncol* **21**:e135. [5]Elsayed (2021) *Biomedicines* **9**:389. [6]Tahkola (2021) *Sci Rep* **11**:12216.

Retinoblastoma

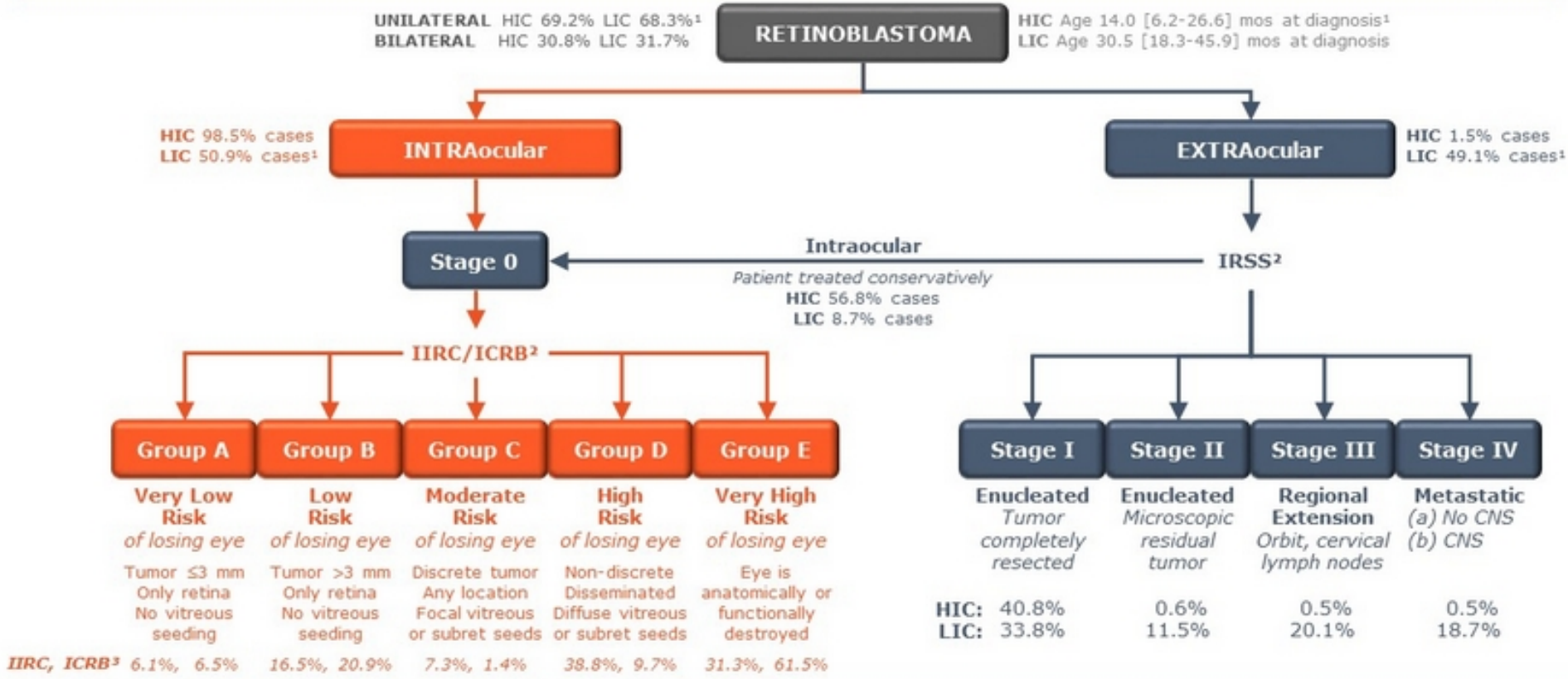
- Retinoblastoma (**Rb**) is a rare pediatric malignancy accounting for ~2-3% of all childhood cancers[1]
  - Primarily diagnosed in children ≤2 years[1]
  - 200-300 cases each year in the USA, EU and >1,000 cases each in China and India[2,3]
  - Significant regional disparities in age/stage at diagnosis, treatment options, and mortality (40-70% mortality in low-income countries cf. 3-5% in high income countries)[4-7]
- Rb can be unilateral (60-70% of cases) or bilateral (30-40%)[4,8]
  - Unilateral disease: 85% of cases have a somatic RB1 mutation, 15% have a germline (heritable) mutation
  - Bilateral disease: assumed that 100% have a germline mutation
- Rb treatments vary with stage of disease[4]
  - Prior to intraarterial chemotherapy (**IAC**), enucleation was the primary life-saving intervention for Rb patients
  - IAC, where available, has dramatically reduced enucleation rates (from >95% pre-IAC to <10%)[9]
- Multiple potential opportunities for VCN-01 in Rb treatment
  - Improve outcomes of surgery and/or chemotherapy (potential reduction in intensity)
  - Rescue therapy to prevent enucleation

[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 slides 34-36. [5]Tomar (2020) *Ophthalmology* **127:**1719. [6]Fabian (2020) *JAMA Oncol* **6:**685. [7]Canturk (2010) *Br J Ophthalmol* **94:**1432. [8]https://eyewiki.org/Retinoblastoma. [9]Abramson (2015) *PLoS ONE* **10:**e0145436.

Rb Cases - One Retinoblastoma World Map[1]

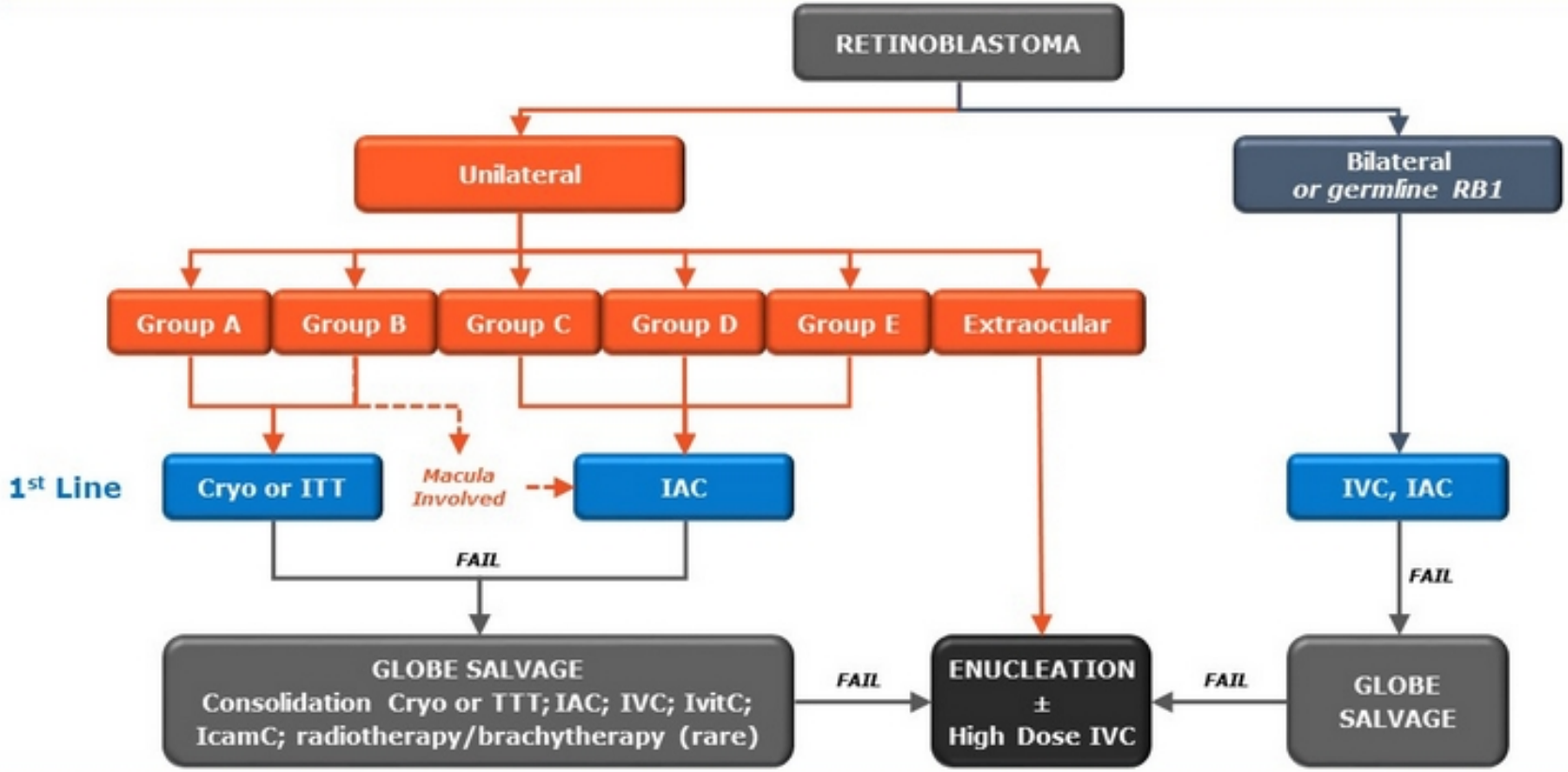
[1]Reported number of retinoblastoma cases from One Retinoblastoma World Map https://map.1rbw.org/ (accessed April-November 2021)

Retinoblastoma Staging



¹Fabian (2020) *JAMA Oncol* **6**:685; median [IQR] age; ²Fabian ID (2018) *Community Eye Health* **31**:11. ³Tomar (2020) *Ophthalmology* **127**:1719. **HIC** high income countries; **ICRB** International Classification of Retinoblastoma. **IIRC** International Intraocular Retinoblastoma Staging System. **IRSS** International Retinoblastoma Staging System. **LIC** low-income countries. **Subret** subretinal.

Retinoblastoma Treatment



Adapted from: Ancona-Lezama (2020) *Indian J Ophthalmol.* **68:**2356. **Cryo** cryotherapy. **IAC** intraarterial chemotherapy (melphalan±topotecan, carboplatin). **IcamC** intracameral chemotherapy (melphalan, topotecan). **IVC** intravenous chemotherapy (vincristine+etoposide+carboplatin). **IvitC** intravitreal chemotherapy (melphalan, topotecan). **TTT** transpupillary thermotherapy.