

TPS 4210 VIRAGE: A Phase IIb, Open-Label, Randomized Study of Nab-Paclitaxel and Gemcitabine plus/minus VCN-01 in Patients with Metastatic Pancreatic Cancer



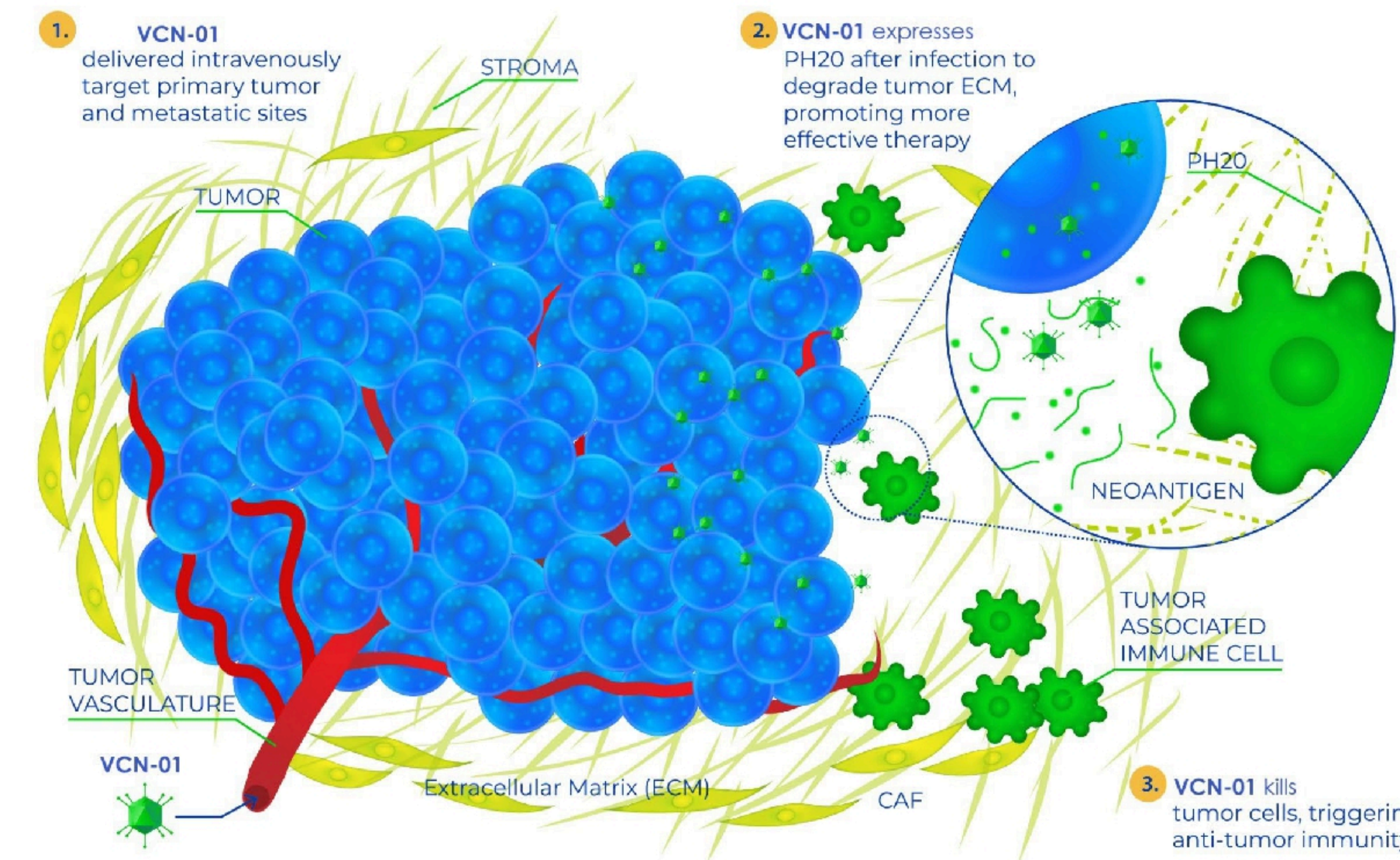
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BACKGROUND

VCN-01 is a modified oncolytic adenovirus type 5 (Ad5) designed to replicate selectively in cancer cells with a dysfunctional RB1-E2F pathway and to express hyaluronidase to degrade the tumor matrix and thereby enhance virus intratumoral spread and facilitate chemotherapy and immune cells extravasation into the tumor.



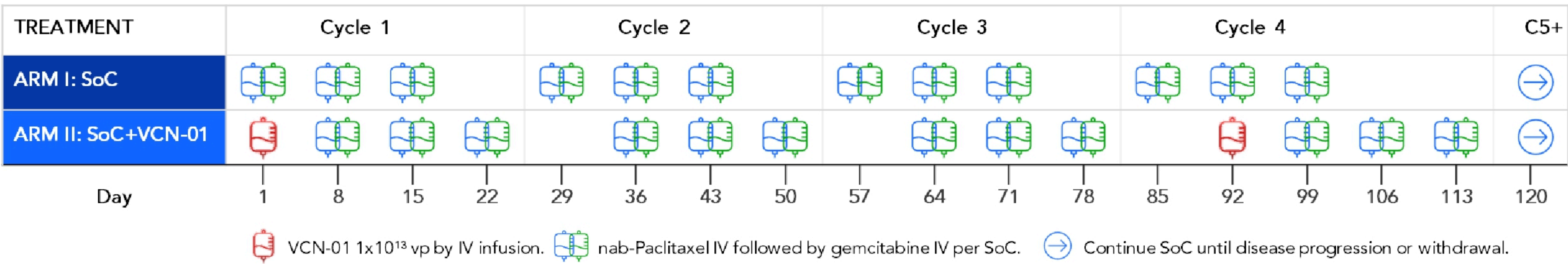
Results obtained in a previous phase I trial in patients with solid tumors showed that a single systemic administration of VCN-01 is feasible and has an acceptable safety profile alone or when combined with standard of care chemotherapy (SoC) nab-paclitaxel plus gemcitabine [NCT02045602]. VCN-01 replicated in tumors and encouraging biological and clinical activity were observed when administered in combination with SoC to patients with metastatic pancreatic adenocarcinoma (mPDAC). In patients administered VCN-01 7-days prior to initiation of SoC, a partial response was observed in 6 out of 12 patients (50%): 1 out of 6 at a VCN-01 dose of 3.3x10¹² vp and 5 out of 6 at 1x10¹³ vp. Median PFS and OS were 6.7 months and 13.5 months respectively. 8 patients (66.7%) survived more than 12 months. A subgroup analysis of patients at the RP2D (1x10¹³ vp) showed an ORR of 83% with a median PFS of 6.3 months and median OS of 20.8 months. Phase I trial also evidenced that anti-adenovirus antibodies (NAb) decreased significantly 3 months after a single VCN-01 dose. Consequently, a second VCN-01 dose may improve treatment outcome.

OBJECTIVES

- Primary:**
- To evaluate the time from randomization to death in both arms (OS).
 - To evaluate the safety and tolerability of VCN-01, intravenously (IV) administered at Week 1 and Week 14 in Arm II.
- Secondary:**
- To evaluate the time to progression (TTP) or progression free survival (PFS).
 - To determine the Objective Response rate (ORR).
 - To determine the disease control rate (DCR) (stable disease [SD] + partial response [PR] + complete response [CR]).
 - To determine the landmark 1-year survival and PFS at the 1 year landmark.
 - To evaluate the duration of response (DoR).
 - To assess changes in tumor marker carbohydrate antigen (Ca) 19.9 measured every 4 weeks while on study.
- Exploratory:**
- Evaluate 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).
 - Radiomic analysis of computerized tomography (CT) images.
 - Characterize the Quality of Life (QoL) via the validated European Organization for Research and Treatment Quality of Life Questionnaire (EORTC) QLQ-C30 questionnaire (version 3).
 - Determine the disease control rate (DCR) (stable disease [SD] + partial response [PR] + complete response [CR]) to the subsequent anti-cancer therapies.

METHODS – STUDY DESIGN

- VIRAGE [NCT05673811] is an international multicenter, open-label, randomized controlled trial evaluating VCN-01 in combination with chemotherapy in patients with **first-line** metastatic pancreatic ductal adenocarcinoma.
- Patients are **randomized 1:1** to receive gemcitabine/nab-paclitaxel (SoC) or up to **two doses** of VCN-01 plus SoC.
- Assuming an accrual time of 18 months with a minimum 12-month follow-up for all patients, the median OS=10.6 months for Arm I and the median OS=20.8 for Arm II with 1: 1 randomization, **46 patients are needed for each arm** to reach the number of events required using the log-rank test with 1-sided alpha = 0.05 and 80% power.
- The trial is expected to enroll **92 evaluable patients** who are currently being enrolled at sites in Spain and the USA.



- Quality of Life (QoL) is measured on Day 1 of Cycle 1 and then once every cycle thereafter.
- Biological markers for **VCN-01 bioactivity** include the quantification of:
 - VCN-01 genomes in blood (Arm II only)
 - PH20 in serum (Arm II only)
 - Circulating immune markers in serum
 - Neutralizing anti-VCN-01 antibodies (Anti-Ad NABs) in serum (Arm II only)
 - Image biomarkers (radiomics) assessed from the images of CT scans
- First **Data Monitoring Committee** safety review was completed Q1 2024.
- Completion of VIRAGE study enrollment is projected during **Q3 2024**.

KEY INCLUSION CRITERIA

- Male/female patients aged 18 years or older.
- Patients with histologically/cytologically confirmed, first line metastatic pancreatic adenocarcinoma stage IV de novo, who never received previous systemic treatment for their pancreatic cancer for which the established therapy is nab-paclitaxel/gemcitabine. Patients must have measurable tumor lesions that can be imaged and assessed by RECIST 1.1
- Patients with a minimum life expectancy of 5 months.
- ECOG performance status of 0 or 1.
- Use of reliable contraception methods in fertile men & women
- Adequate baseline organ function (hematologic, liver, renal and nutritional) verified within 72 hours prior to dosing:
 - Hematology:
 - Absolute neutrophil count ≥1.5x10⁹/L & Platelets ≥100x10⁹/L
 - Hemoglobin ≥9 g/dL
 - Coagulation:
 - Prothrombin time (PTT) or international normalized ratio (INR) ≤1x upper limit of normal (ULN)
 - Activated partial thromboplastin time (APTT) ≤1.2xULN
 - Hepatic:
 - Total bilirubin ≤1.5xULN
 - ALT and AST ≤2.5xULN (if there are NO liver metastases) or ALT and AST <5xULN and bilirubin <1.5xULN if there ARE liver metastases)
 - Renal:
 - Serum creatinine ≤1.5xULN and if >1.5xULN
 - Nutritional:
 - Serum Albumin ≥30 g/L

KEY EXCLUSION CRITERIA

- Active infection or other serious illness or autoimmune disease at randomization.
- Treatment with live attenuated vaccines.
- Known chronic liver disease.
- Treatment with another investigational agent within five of that treatment’s half-lives prior to infusion of treatment.
- Viral syndrome diagnosed during the 2 weeks before start of study treatment administration.
- Chronic immunosuppressive and/or disease modifying therapy, except corticosteroids with a dose lower than defined.
- Concurrent malignant hematologic or solid disease.
- Patients in close contact with immunosuppressed patients.
- Patients with Li Fraumeni syndrome or with known retinoblastoma protein pathway germline deficiency.
- A female patient, who is pregnant or lactating.
- Patients receiving full-dose anticoagulant therapy or in whom these therapies cannot be withdrawn 2 days prior and 2 days after VCN-01.
- Untreated brain metastases and/or leptomeningeal carcinomatosis with progressive symptoms
- Patients with previous pneumonitis / interstitial lung disease
- Patients with pre-existing sensory neuropathy >G1.
- Patients with risk factors for bowel perforation.
- Subjects, for whom first line treatment options other than the combination Gemcitabine/Nab-Paclitaxel are recommended by the investigator.

DISCLOSURES

CL, MK, MAS, CB, and MC are employees of Theriva Biologics. MC is founder of Theriva Biologics, S.L.

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REFERENCES

1. 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.
2. Bazan-Peregrino M et al. (2021) VCN-01 disrupts pancreatic cancer stroma and exerts antitumor effects. J ImmunoTher Cancer 9:e003254.