1231P: Phase I Study to Evaluate the Safety, Tolerability, and Efficacy of VCN-01 in Combination With Durvalumab (MEDI4736) in Subjects With Recurrent/ Metastatic Squamous Cell Carcinoma of the Head and Neck (R/M HNSCC)

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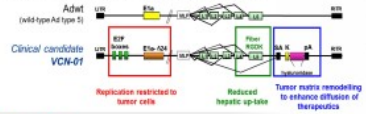
Background

VCN-01 is an oncolytic adenovirus designed to replicate selectively in cancer cells. It expresses a matrix remodeling-enzyme hyaluronidase and increases immune check-point antibody uptake in preclinical models. It also induces a pro-inflammatory tumor environment after intravenous [i.v] administration in pancreatic cancer patients (pts). VCN-01 may help to overcome previous resistance to anti-PD(L)-1 therapies in patients with R/M HNSCC.



Hypothesis

Systemic administration of VCN-01 will lead to intratumoral viral replication causing tumor inflammation, PD-1/PD-L1 up-regulation and strong CD8-infiltration. These intratumor effects may help to overcome resistance to PD-(L)-1 checkpoint inhibitors (alone or in combination) in patients who have progressed during or after treatment with immune-checkpoint inhibitors

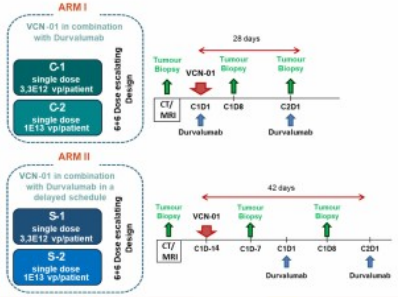
Objective

NCT03799744 is a multi-center, open-label dose-escalation phase I study to investigate the safety and tolerability of intravenous VCN-01 with Durvalumab in the two regimens of administration and to establish the recommended phase II dose.

Trial Design & Methods

Phase I dose-escalation study testing two dose levels of i.v. VCN-01 (3,3E12 & 1E13 viral particles, [vp]) combined with a fixed dose of Durvalumab (1500 mg) using 3+3 design in R/M HNSCC pts previously treated with antiPD(L)-1 agents. Two treatment schedules were explored: concomitant (single dose VCN-01 and Durvalumab on day 1, CS), and sequential (single dose of VCN-01 on day -14 and Durvalumab on day 1; SS), both followed by Durvalumab q4 weeks until progression or intolerable toxicity. Fresh tumor biopsies were taken at baseline, post-VCN-01 and post-Durvalumab

Study Population: Patients with metastatic squamous cell carcinoma of the head & neck who have progressed during or after treatment with immune-checkpoint inhibitors. Eligibility Criteria included the selection of patients with levels of neutralizing antibodies against adenovirus <1/350 dilution at the moment of inclusion in the study



Results

Safety profile of VCN-01

Characteristics		Concomitant Arm I-1 3,3E12 vp (n = 6)	Sequential Arm II-1 3,3E12 vp (n = 3)	Sequential Arm II-2 1E13 vp (n = 6)
Age, years (Median (Range))		54 (22-66)	63 (37-79)	62 (54-73)
Sex (Male / Female)		5/1	0/0	3/3
ECOG	0	1	1	3
	1	5	7	3
Tobacco	yes	1	1	0
	no	1	0	3
	former	4	7	3
Anatomic Site	Oral Cavity	3	5	2
	Oropharynx	1	2	1
	Larynx	2	1	1
	Hypopharynx	0	0	1
Previous /CI	Anti PD-1	5	6	5
	Anti PD-L1	1	2	1
TNM at study entry:	IVa	1	2	3
	IVb	0	0	1
	IVc	3	2	1
	unk	2	4	0

Table 1: Patient demographics and clinical characteristics

Adverse Reactions CTCAE Grade	Arm I (Concomitant, 6) Grade 1-2	Arm I (Concomitant, 6) Grade ≥3	Arm II (Sequential, 14) Grade 1-2	Arm II (Sequential, 14) 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%)

Table 2: VCN-01 Related AEs *(except Grade 1-2 observed in n=1)*

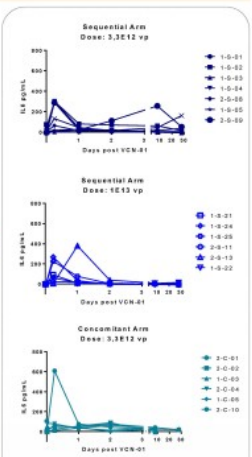


Figure 1: IL 6 levels were analyzed in serum from patients treated with VCN-01 at different time points.

Pharmacokinetics and pharmacodynamics of VCN-01

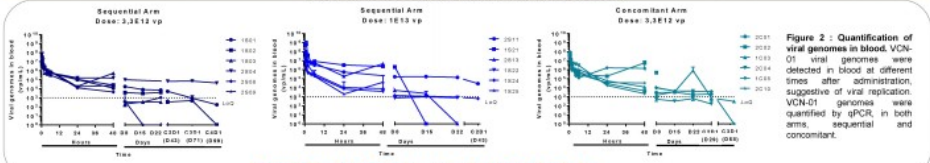


Figure 2 : Quantification of viral genomes in blood. VCN-01 viral genomes were detected in blood at different times after administration, suggestive of viral replication. VCN-01 genomes were quantified by qPCR, in both arms, sequential and concomitant.

Sustained levels of viral genomes are observed in all patients

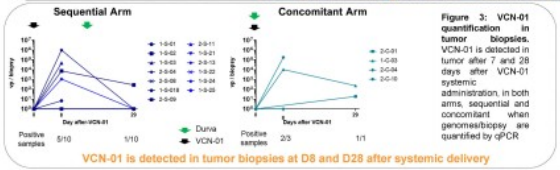


Figure 3: VCN-01 quantification in tumor biopsies. VCN-01 is detected in tumor after 7 and 28 days after VCN-01 systemic administration, in both arms, sequential and concomitant when genomes/biopsy are quantified by qPCR

VCN-01 is detected in tumor biopsies at D8 and D28 after systemic delivery

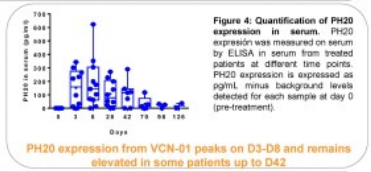


Figure 4: Quantification of PH20 expression in serum. PH20 expression was measured on serum by ELISA in serum from treated patients at different time points. PH20 expression is expressed as pg/mL minus background levels detected for each sample at day 0 (pre-treatment).

PH20 expression from VCN-01 peaks on D3-D8 and remains elevated in some patients up to D42

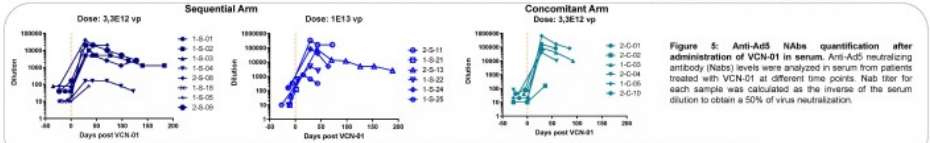


Figure 5: Anti-Ad5 NAbs quantification after administration of VCN-01 in serum. Anti-Ad5 neutralizing antibody (NAbs) levels were analyzed in serum from patients treated with VCN-01 at different time points. Nab titer for each sample was calculated as the inverse of the serum dilution to obtain a 50% of virus neutralization.

Anti-Ad5 NAbs after VCN-01 peak on D28, then start decreasing over time, reaching a ~1-2 log reduction by D150

Mechanism of action of VCN-01 induces changes in tumor microenvironment

Immunohistochemistry

	CD8 /Treg axis	PD-1 / PD-L1 axis	IFNγ/ 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)		

Table 3: 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

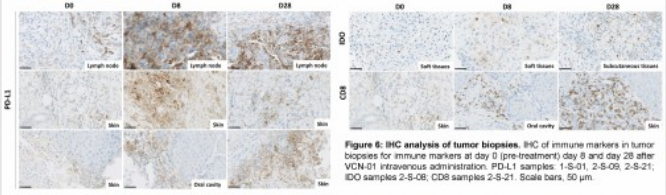


Figure 6: IHC analysis of tumor biopsies. IHC of immune markers in tumor biopsies for immune markers at day 0 (pre-treatment) day 8 and day 28 after VCN-01 intravenous administration. PD-L1 samples: 1-S-01, 2-S-09, 2-S-21; IDO samples 2-S-08; CD8 samples 2-S-21. Scale bars, 50 µm.

VCN-01 modulates tumor microenvironment inducing up-regulation of PD-L1, CD8 and IDO in tumor cells

Transcriptomic analysis

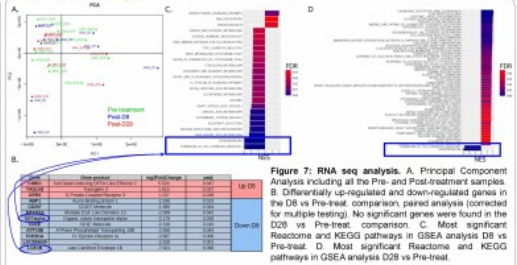


Figure 7: RNA seq analysis. A. Principal Component Analysis including all the Pre- and Post-treatment samples. B. Differentially up-regulated and down-regulated genes in the D8 vs Pre-treat. comparison, paired analysis (corrected for multiple testing). No significant genes were found in the D28 vs Pre-treat. comparison. C. Most significant Reactome and KEGG pathways in GSEA analysis D8 vs Pre-treat. D. Most significant Reactome and KEGG pathways in GSEA analysis D28 vs Pre-treat.

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

Radiomics

T2 relaxation time (n=20) → No differences. The percentile 25% of T2, was close to be statistically significant, (p-value =0.06349)

- *DWI biomarkers (n=16) (D* & D, perfusion & diffusion components, respectively) → No differences between treatment arms*
- *DCE biomarkers (n=11):*
  - *V transfer constant plasma → extravascular/extracellular space (EES) (K_{trans}) → reduced dispersion on sequential vs. concomitant (p=0.014)*
  - *rate transfer constant extravascular space ↔ blood (K_{ep}) → increased value on sequential group vs. concomitant-treated patients (p=0,022)*

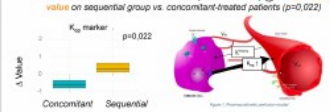


Figure 8: Analysis of radiomics markers from MRIs. T2* sequences, Diffusion weighted imaging (DWI) and Dynamic contrast enhanced (DCE) were acquired from MRI images using 1.5T and 3T equipment. Imaging biomarkers were obtained by a non-invasive imaging post-processing procedure. The delta (Δ) radiomic 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

Conclusions

Treatment with VCN-01 is feasible with an acceptable safety profile when administered with Durvalumab in a sequential schedule. Based on PK/PD and toxicity, VCN-01 RP2D is 1E13vp. Encouraging biological activity is observed in R/M HNSCC pts.

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