A Phase I Open-Label Study to Evaluate Safety, Tolerability and Pharmacokinetic (PK) Profile of VB4-845, an anti-Ep-CAM Immunotoxin, in Subjects with SCCHN

Abstract #5539

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Updated Abstract

Background: VB4-845 (Proxinium™) is a recombinant protein engineered from the fusion of a humanized scFv specific for the epithelial cell adhesion molecule (Ep-CAM) to a truncated form of *Pseudomonas* Exotoxin A (ETA). Ep-CAM is highly expressed on carcinoma cells of epithelial origin, with limited normal cell expression. VB4-845 selectively targets and kills Ep-CAM-positive tumors. A phase I dose-escalation trial was completed to determine the safety, tolerability, pharmacokinetic (PK) profile and preliminary efficacy of intratumorally injected VB4-845 in patients with advanced Squamous Cell Carcinoma of the Head and Neck (SCCHN).

Methods: Dose escalation was completed using an accelerated two-stage dose escalation design: A dose doubling with 1-3 patients per dose cohort followed by a modified Fibonacci escalation scheme. A minimum of 3 patients were enrolled per dose cohort. VB4-845 was administered over 5 consecutive days by intratumoral injection at escalating dose levels of 20, 40, 80, 130, 200, and 280 µg/day. After a 23 day rest, a 2nd cycle of VB4-845 was given at each dose level. Dose escalation could proceed once the patients in the previous dose cohort had completed one full cycle of treatment without experiencing dose limiting toxicity. The lesion of longest diameter and suitable for accurate repeated measurements was injected with VB4-845. All toxicities were assessed according to the NCI Common Toxicity Criteria. Blood samples were collected at different times in the study to determine PK and to assess the immunogenicity of VB4-845. CT scans and tumor volume measurements where analyzed in order to assess the efficacy of VB4-845 administration in this patient population.

Results: A total of 24 patients were enrolled onto this study. Dose escalation proceeded to the highest planned dose (280 µg/day). No maximum tolerated dose (MTD) was reached. The safety profile was favorable with only mild treatment-related side-effects, such as injection site pain and transient, reversible liver function tests noted. PK analysis of intratumorally injected VB4-845 demonstrated a clearance rate of 3-4 hours. Most patients developed systemic anti-VB4-845 antibody titers, with most of these responses directed against ETA. Independently-verified clinical responses were observed in 43% of the patients with Ep-CAM positive tumors. Four other patients with Ep-CAM-positive tumors had stable disease, for an overall tumor growth control rate (objective responses plus stable disease) of 71%. All Ep-CAM negative patients progressed on study.

Conclusions: VB4-845 administered on a monthly schedule of 5 consecutive days dosing followed by 23 days rest was found to be safe and tolerable at all dose levels tested, suggesting that higher dose levels could be explored. An MTD was not reached. Moreover, although this study was primarily designed to evaluate safety and tolerability, clinical endpoints indicate that VB4-845 treatment showed promising efficacy against Ep-CAM-positive SCCHN tumors in a highly treatment-refractory patient population, thus warranting further development.

Background

- Head and neck cancer is the sixth most common cancer (~5% of newly diagnosed malignancies in North America)
- VB4-845 is a recombinant protein engineered from the fusion of a humanized scFv antibody fragment specific for the epithelial cell adhesion molecule, Ep-CAM, to a truncated form of *Pseudomonas* Exotoxin A (ETA)
- Ep-CAM is highly expressed on carcinoma cells of epithelial origin including Squamous Cell Carcinoma of the Head and Neck, and has limited normal cell expression
- Mechanism of action:
  - VB4-845 selectively binds to Ep-CAM-positive tumors and is internalized by the tumor cell through an endocytic pathway
  - The ETA portion of VB4-845 is then:
    - Efficiently dissociated within the endosome
    - Trafficked to the endoplasmic reticulum
    - Shuts off protein synthesis via binding to ribosomal eF2
    - Results in tumor cell death via apoptosis
- A phase I trial was completed to determine the maximum tolerated dose (MTD) and the PK profile of intratumorally injected VB4-845 in patients with advanced squamous cell carcinoma of the head and neck (SCCHN)

Objectives

Primary

- To determine the maximal tolerated dose (MTD) of intratumorally injected VB4-845 when injected for 5 consecutive days followed by 23 days of rest (cycled twice)

Secondary

- To determine the safety and feasibility of intratumorally injected VB4-845
- To evaluate the tumor-response of intratumorally injected VB4-845
- To evaluate the pharmacokinetic profile of intratumorally injected VB4-845

Eligibility

Principal Inclusion Criteria

- Histologically confirmed diagnosis of advanced squamous cell carcinoma of the head and neck (SCCHN) that has recurred after radiotherapy and/or chemotherapy
- Measurable disease of at least one amenable target lesion
- Age ≥ 18 years, signed informed consent
- Karnofsky performance status of ≥ 70
- Estimated life expectancy > 3 months
- Adequate hepatic, hematological and renal function

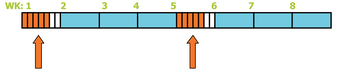
Principal Exclusion Criteria

- Clinical evidence of brain metastases
- Suspected or impeding airway obstruction
- Suspected or documented carotid artery infiltration of the lesion to be injected
- HIV, Hepatitis C (HCV), Hepatitis B
- Treatment with any other monoclonal antibody or investigational product within 4 weeks prior to screening visit
- Uncontrolled hypertension
- Radiation therapy or systemic corticosteroids within 4 weeks prior to screening visit

Trial Design

Phase I, open-label, single arm, safety and tolerability study in ascending dose cohorts with a 2-phase dose escalation scheme

- 6 planned dose cohorts:
  - dose doubling starting at 20 µg, 40 µg and 80 µg per day in an accelerated approach (1-3 patients per dose cohort) followed by
  - Fibonacci escalation at 130 µg, 200 µg and 280 µg per day (at least 3 patients per dose cohort)
- 24 patients enrolled in 8 months



- 5 consecutive days followed by 23 days rest
- Two cycles, 8 weeks total
- Dose escalation decision after review of safety and tolerability of first cycle of treatment (28 days)
- PK assessments on Day 1 of Cycle 1 (pre-dose, 10 min,30 min, then at 1,2,4,6,12 and 24 hrs following first dose) and a single pre-dose sample on Day 5 of Cycle 1 and Day 1 of Cycle 2
- Anti-VB4-845 antibodies measured on Days 7, 14 and 21 of Cycle 1 and Day 1 of Cycle 2 (pre dose)
- Safety assessed from AEs, lab results, physical examination, vital signs, chest X-Ray, ECG, pain assessment
- Objective tumor responses assessed from tumor measurements by caliper, CT Scans and digital photography

Definition of Maximum Tolerated Dose (MTD)

- The dose at which 2 patients experience a dose-limiting toxicity (DLT) as evaluated within their first cycle of treatment

A DLT was defined as any drug-related:

- Grade 4 toxicity for local reaction due to intratumoral injection
- Grade 4 flu-like symptom
- Grade 4 hematological toxicity
- Any other grade 3 non-hematological toxicity

Patient Characteristics (N=24)

Age – median (range)	65 years (48-77)
Gender	
Male	19
Female	5
Race	All Caucasian
Karnofsky Performance Status	
70	1
70-80	21
90	2
Prior Therapy	
Chemotherapy	16
1 Cycle	2
2 Cycles	2
3 Cycles	12
Radiotherapy	24

Treatment Summary

Dose (µg/day)	Number of patients
20	2
40	3
80	2
130	8
200	3
280	6

Top planned dose reached – no dose-limiting MTD

Most Common Adverse Events (N=16)

	Number of patients per grade*			
	Grade 1	Grade 2	Grade 3	Grade 4
Tumor Pain	2	4	3	
Pain due to Intratumoral Injection		7		
Elevated Liver Function Tests		2	3	1
Tumor Bleeding			2	1
Dysphagia		1	2	
Weight Loss	3			

* In the situation where a subject may have had an AE more than once, the AE with the highest grade level was accounted

Adverse Events Related to Study Drug

Number of patients with Adverse Events Related to Study Drug (N=11)

	Number of patients per grade*			
Adverse event	Grade 1	Grade 2	Grade 3	Grade 4
Pain due to Intratumoral Injection		7		
Transient and Reversible Elevated Liver Function Test		1	2	1
Tumor Pain	1		1	

* In the situation where a subject may have had an AE more than once, the AE with the highest grade level was accounted

VB4-845 was safe and well-tolerated

Pharmacokinetics

Dose Level (µg)	# of Patients[1]	Cmax (pg/mL)	Tmax (h)	$AUC_{0\text{-last}}$ (pg/mL*h)	$T_{1/2}$ (h)
20	1	18	0.16	59	3.76
40	1	202	4	1407	4.6
80	2	102	3	1039	4.73
130	4	1051	2.17	3132	2.6
200	2	258	2.08	1203	4.66
280	5	2646	0.76	7847	3.46

VB4-845 plasma concentration was measured using an MTS-based assay to determine cytoxicity against the SCCHN cell line Cal-27. [1]Indicates number of patients in each dose level that had a detectable level of VB4-845. Where >1 patient at a given dose level had detectable VB4-845 in the plasma, the values reported are the mean.

- Only 15 of the 24 patients had detectable levels of VB4-845
- 7 of the 9 patients where VB4-845 could not be detected in the plasma had a pre-existing HAPA response
- The mean Cmax (peak VB4-845 exposure) ranged from 18 to 2646 pg/mL and corresponding Tmax ranging from 10 min to 130 min
- The mean extent of exposure (AUC0-last) ranged from 59 to 7847 pg/mL*h.
- The mean half-life (T1/2) of VB4-845 at each dose level ranged from 2.9 to 5.1 hours with a mean half-life across all doses being 4.0±0.3 hrs.

Immunogenicity of Proximium: HAPA and HAHA responses

Day	HAPA		HAHA	
	# Patients	Titer Range ($x10^{-3}$)	# Patients	Titer Range ($x10^{-3}$)
0	14/25	1-8	ND	ND
7	12/25	2 - 1.6x10^3	4/25	1 - 12
28	19/22	1.5 - 1.2x10^5	4/22	1 - 135
56	21/21	2 - 1.6x10^7	18/21	1 - 74.1

Plasma samples were collected at different time points and assessed for HAPA and HAHA responses using an ELISA-based assay. Antibody titer is defined as the reciprocal of the greatest dilution of sera giving a positive OD (OD blank+4SD).

- 14 patients had measurable pre-bleed antibody titers to *Pseudomonas* exotoxin A (anti-ETA or HAPA response)
- All patients tested had developed a HAPA response by the end of the study
- Most of the patients eventually developed a HAHA response by the end of the study but the titer was much lower than the HAPA response

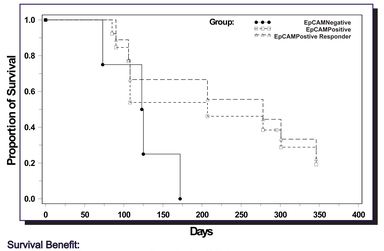
Summary of Response Data By Ep-CAM Positivity

	Response	Stable	Progression	Non-evaluable	Total
Total number of patients Ep-CAM positive (N)	6	4	4	3	17
Percentage Ep-CAM positive (%)	35	23.5	23.5	18	100
Percentage Ep-CAM positive and Evaluable (%)	43	28.5	28.5	-	100
Total number of patients Ep-CAM negative (N)	0	0	6	1	7
Percentage Ep-CAM negative (%)	0	0	86	14	100
Percentage Ep-CAM negative and Evaluable	0	0	100	-	100

Overall Response in Evaluable Ep-CAM positive patients:

- 43% Objective Response
- 71% Tumor Growth Control Rate (objective response + stable disease)

Survival Analysis by Ep-CAM Status



Survival Benefit:

- Ep-CAM negative: mean overall survival – 125 days
- Ep-CAM positive: mean overall survival – 207 days
- Ep-CAM positive responders: mean overall survival – 301 days
- To date: 3 out of 14 evaluable Ep-CAM positive patients are still alive (295+ - 456+ Days)
- No Ep-CAM negative patients still alive

Summary and Conclusions:

- VB4-845, a recombinant fusion protein specific to Ep-CAM, can be safely and repeatedly administered to patients with advanced SCCHN via intratumoral injection, on a monthly schedule of administration (5 consecutive days of dosing with 23 days rest).
- No maximum tolerated dose reached
- Half-life of VB4-845 was determined to be approximately 4 hrs
- Systemic anti-VB4-845 antibodies were produced within 7 days of administration
- Although not designed to establish efficacy, this study demonstrated a 43% objective response rate with a 71% overall tumor growth control rate for Ep-CAM positive patients in this advanced, therapy-resistant patient population
- Survival data trend suggests that VB4-845 administration has the potential to increase overall survival in this advanced patient population
- These promising safety and efficacy results support further clinical development of VB4-845.

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Investigator Name	Investigator Address
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