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ORIGINAL RESEARCH

A Phase I study of an intravesically administered immunotoxin targeting EpCAM for the treatment of nonmuscle-invasive bladder cancer in BCG-refractory and BCG-intolerant patients

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Purpose: A Phase I dose-escalation study was performed to determine the maximum tolerated dose (MTD) of the immunotoxin VB4-845 in patients with nonmuscle-invasive bladder cancer (NMIBC) refractory to or intolerant of *bacillus* Calmette–Guerin (BCG). Secondary objectives included evaluation of the safety, tolerability, pharmacokinetics, immunogenicity, and efficacy of VB4-845.

Patients and methods: Sixty-four patients with Grade 2 or 3, stage Ta or T1 transitional cell carcinoma or in situ carcinoma, either refractory to or intolerant of BCG therapy, were enrolled. Treatment was administered in ascending dose cohorts ranging from 0.1 to 30.16 mg. After receiving weekly instillations of VB4-845 to the bladder via catheter for 6 consecutive weeks, patients were followed for 4–6 weeks post-therapy and assessed at week 12.

Results: An MTD was not determined, as a dose-limiting toxicity was not identified over the dose range tested. VB4-845 therapy was safe and well tolerated with most adverse events reported as mild; as a result, no patients were removed from the study in response to toxicity. By the end of the study, the majority of patients had developed antibodies to the exotoxin portion of VB4-845. A complete response was achieved in 39% of patients at the 12-week time point.

Conclusions: VB4-845 dosed on a weekly basis for 6 weeks was very well tolerated at all dose levels. Although an MTD was not determined at the doses administered, VB4-845 showed evidence of an antitumor effect that warrants further clinical investigation for the treatment of NMIBC in this patient population.

Keywords: *Pseudomonas* exotoxin A, anti-EpCAM, fusion protein, targeted therapy

Introduction

Bladder cancer is the fourth most common malignancy in men and the ninth most common in women, with an estimated incidence of 67,160 and 13,750 estimated deaths (2007) in the United States. Transitional cell carcinoma (TCC) refers to those bladder cancer tumors derived from urothelial tissue, more than 90% of which originate in the urinary bladder and present as nonmuscle-invasive disease in the majority of patients at diagnosis.[1] Of those patients who respond to current standard of care, approximately two-thirds will have recurrence, and 10%–20% of recurrent tumors will have progressed to muscle-invasive disease.[2] Typically, treatment for high-risk, nonmuscle-invasive bladder cancer (NMIBC) is transurethral resection of the bladder tumor and adjuvant therapy with *bacillus* Calmette–Guerin (BCG). Although BCG treatment can reduce the risk of recurrence and progression, its use is limited by the adverse effect profile and intolerance that occurs in 20% of patients.[3–6]

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Epithelial cell adhesion molecule (EpCAM) is overexpressed in many carcinomas relative to their normal tissue counterparts, as is the case in TCC.[7,8] In addition, EpCAM expression increases as these cancers progress from lower to higher grades.[8–11] Together, these features make EpCAM a clinically relevant antigen for targeted therapy in bladder cancer.

VB4-845 is a recombinant fusion protein that targets EpCAM-positive cancer cells. It consists of an anti-EpCAM humanized single-chain variable fragment (scFv) linked to a truncated form of *Pseudomonas* exotoxin A ($ETA_{252–608}$) that lacks the cell-binding domain.[12] Once bound to EpCAM on the surface of carcinoma cells, VB4-845 is internalized, whereupon the exotoxin portion of the fusion protein induces apoptosis.[13,14]

One concern of targeted therapies has been the toxicity associated with systemic administration of this class of drug.[15] Moreover, repeated use of therapeutics comprising foreign proteins is limited by their immunogenicity. Therefore, it is desirable to develop therapies designed for local administration, thereby increasing the clinical benefit of these treatments while minimizing any drug-related effects. Accordingly, locoregional delivery of ETA-conjugated antibodies has been demonstrated to be well tolerated and clinically effective in patients with glioblastoma multiforme, ErbB2-expressing breast tumors, and squamous cell carcinoma of the head and neck.[16–18] Nonclinical studies showed a significant reduction in toxicity with locally administered VB4-845. Similarly, local injections of VB4-845 were well tolerated in Cynomolgus monkeys with adverse events (AEs) being mild and easily managed.[19] In addition to the strong nonclinical safety profile, VB4-845 exhibits highly potent activity against EpCAM-expressing tumor cell lines and has been shown to localize to EpCAM-positive tumor xenografts.[12] Based on these preclinical results, a Phase I dose-escalation trial was performed using VB4-845 as an intravesical therapy in BCG-refractory and BCG-intolerant patients with Grade 2 or 3 NMIBC.

Patients and methods

Patient selection

Only patients 18 years of age or older with immunohistochemically confirmed EpCAM-positive Grade 2 or 3 NMIBC (Ta, T1, in situ carcinoma [TIS]), either refractory to (recurrence within 2 years following at least one complete cycle of BCG therapy) or intolerant of BCG therapy, were eligible for this study. Other key inclusion criteria were adequate renal (serum creatinine $\leq 1.5 \times$ the upper limit of normal (ULN) or creatinine clearance $\geq$60 mLs/min), hepatic (alanine aminotransferase and aspartate aminotransferase $\leq 2.5 \times$ ULN and bilirubin levels $\leq 1.5 \times$ ULN), and hematological (granulocytes $\geq$1500/μL, platelets $\geq$100,000/μL, and hemoglobin $>$8 g/dL) function. Women of child-bearing potential, and all men, must have agreed to use adequate contraception prior to and for the duration of the study.

Key exclusion criteria included patients with muscle-invasive tumors, nodal involvement, or distant metastases; patients with a history of upper tract TCC, adenocarcinoma, or squamous cell carcinoma of the bladder; and patients with disease involving the prostatic ducts or stroma. Moreover, excluded were patients with a history of pelvic malignancy, hydronephrosis, or clinically significant abnormalities of the upper urinary tract and those who had undergone BCG therapy within 6 weeks prior to the start of VB4-845 dosing.

Written informed consent was obtained from each participant before any study-related activity was performed. This study was conducted according to Section C.05.010 of Division 5 of the Food and Drug Regulations of the Government of Canada, ICH Harmonized Tripartite Guidelines for Good Clinical Practice, the Declaration of Helsinki (2002), and all local laws and regulations concerning clinical studies and the protection of study patients. Regulatory clearance for the study was obtained from the Biologics and Genetic Therapies Directorate of Health Canada in Canada.

Study design and dose escalation

The study was an open-label, multicenter, dose-escalating trial of intravesically administered VB4-845. Eight dose levels were initially evaluated, starting at 0.1 mg once weekly for 6 consecutive weeks and escalating through 0.2, 0.33, 0.66, 1.32, 2.64, 5.28, and 10.56 mg/dose. The maximum tolerated dose (MTD) was not reached; therefore, an additional escalation through 13.73, 17.85, 23.20, and 30.16 mg was undertaken. Each dose was administered to the bladder through a catheter and held for 2 h prior to voiding. Safety data from each dose cohort was evaluated after 3 weeks of treatment before proceeding to the next dose cohort. Dose-limiting toxicity (DLT) was defined as the occurrence of treatment-related AEs, including intractable cystitis persisting for more than 1 week associated with severe pain, urgency, and/or frequency not relieved by measures considered to be routine standard of care according to each clinical site; significant hematuria leading to clot obstruction; Grade 4 flu-like symptoms; Grade 3 or higher hematological toxicity (if it is a two grade increase from baseline); or any

other Grade 3 nonhematological toxicity (with the exception of alopecia). If two patients experienced a DLT at any dose, that dose would be defined as the MTD.

Patient evaluation

Patients were evaluated at every visit by physical exam and assessment of vital signs. Urinalysis was performed, and blood was collected for biochemistry and hematology. Concomitant medications were recorded. Specific additional evaluations were performed depending on the timing of the visit, as described below.

Pretreatment screening evaluations were conducted within 4 weeks of the baseline visit and included medical history, pregnancy test, 12-lead electrocardiogram, and assessment of Karnofsky performance status. Tumors were evaluated by cystoscopy/photography, cytology, and biopsy. Cytopathology and biopsy pathologic examinations were performed locally and not at a central laboratory. Immunohistochemistry on snap-frozen tissue samples was performed at a single facility to determine whether tumors were EpCAM positive.

In addition to the evaluations performed at every study visit, patients were monitored for AEs for 3 h following drug administration on days 1, 8, 15, 22, 29, and 36. The toxicity grade of any AE was classified according to the National Cancer Institute Common Toxicity Criteria, Version 3. AEs were considered to be treatment related by the investigators if they were possibly, probably, or definitely related to VB4-845 administration. On day 2, AEs and concomitant medications were evaluated by interview.

The last visit occurred 4–6 weeks after the final treatment. Additional assessments performed included pregnancy test, 12-lead electrocardiogram, and Karnofsky performance status. To evaluate tumor response, cystoscopy/photography and cytology were performed. A biopsy was required if the cystoscopy revealed lesions suspicious for malignancy, or cytology results were suspicious or positive for malignancy.

Pharmacokinetics and immunogenicity

Blood samples for pharmacokinetic analysis were taken on day 1 prior to and 1, 2, and 3 h postdosing. Predose samples were also taken on days 8, 15, 22, 29, and 36. For each sample, 3 mL of venous blood was collected into a tube containing lithium heparinate and placed on ice. VB4-845 plasma levels were measured using a GLP-validated, MTS-based, potency assay.[18] The assay detects intact VB4-845 by its ability to kill the EpCAM-positive cell line CAL-27, where the measured IC_{50} is directly proportional to the concentration of intact drug. The assay was shown to have a lower limit of detection of 14 pg/mL.

Blood samples for assessing humoral immune reactivity to VB4-845 were taken prior to dosing on days 1, 8, 15, 22, 29, 36, and at the final study visit. Samples were collected as for the pharmacokinetic analysis, and antibody titers to the scFv and $ETA_{252–608}$ portions of the fusion protein (human anti-human antibodies (HAHA) and human anti-*Pseudomonas* antibodies (HAPA)) were measured using an enzyme-linked immunosorbent assay.[18] Responses were expressed as the geometric mean of measurable titers at each time point.

Evaluation of efficacy

Tumor response was assessed on evaluable patients 4–6 weeks following the last dose of VB4-845. The evaluation was based on cytology, cystoscopy, and, if required, biopsy. Complete response was defined as nonpositive urinary cytology and either normal cystoscopy or abnormal cystoscopy with negative biopsy.

Results

Patient characteristics

Sixty-four patients were enrolled in this study. All participants were Caucasian with a median patient age of 69; 78% were men and 22% were women (Table 1). All patients evaluated for efficacy (61/64) had previously received BCG therapy, with 95% of the patients having had two or more bladder cancer recurrences. Based on their previous BCG treatment

Table 1 Patient characteristics

Characteristic	Number of patients (N = 64)
Gender	
Male	50 (78)[a]
Female	14 (22)
Disease duration	
1–4 years	43 (67)
>4 years	21 (33)
Number of recurrences	
<2	3 (5)
≥2	61 (95)
Prior BCG cycles	
0	2 (3)
1	27 (42)
≥2	35 (55)
Last BCG cycle[b]	
>6 months	40 (63)
≤6 months	22 (34)
Tumor stage at baseline	
Ta	30 (47)
T1	17 (27)
TIS	17 (27)

Notes: [a]Percentages are shown in parentheses. The median patient age was 69 years with patient ages ranging 50–87 years; [b]Two patients had not received BCG.

history, only five patients were considered to have been enrolled as BCG intolerant rather than BCG refractory. All patients had Grade 2 or 3, stage Ta or T1, TCC, and/or TIS, and, except for two cases, all papillary tumors had been previously resected 7–28 days prior to the first dose of study drug. Of note, as this study was carried out prior to the widespread adoption of re-transurethral resection (re-TUR) of TaT1, high-grade NMIBC in clinical practice, and its inclusion in standard treatment guidelines, re-TUR of T1 tumors was not performed. All tumors showed immunohistological evidence of EpCAM-positive membrane staining (Figure 1). Risk factors for progression present in the patient population are summarized in Table 2. At baseline, 98% of patients had at least one factor associated with disease progression, and 64% of these individuals had three or more risk factors.

Dose escalation and MTD

VB4-845 was administered to the bladder via catheter once a week for 6 consecutive weeks, followed by 4–6 weeks without treatment. An MTD was not determined from the initial dose escalation as no DLT was reported; therefore, additional dose cohorts were added as described above, and, again, all patients received all six scheduled doses without any DLT. The number of patients per dose cohort is summarized in Table 3.

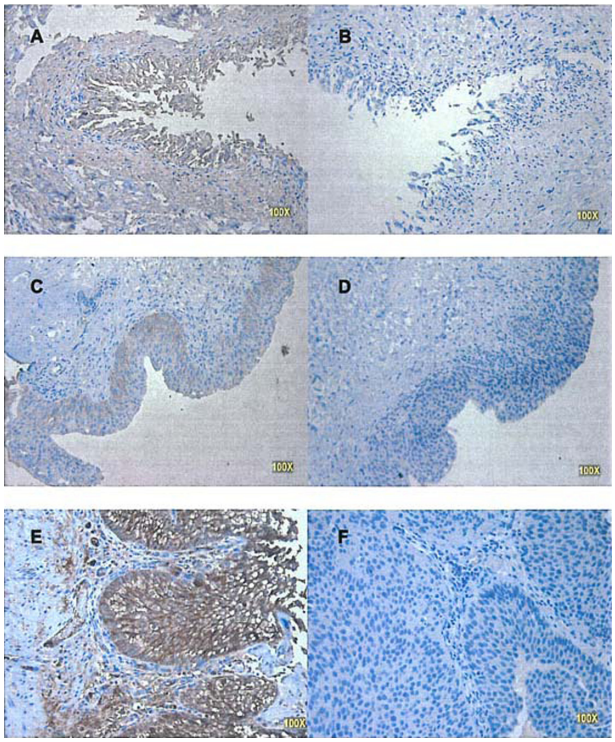

Figure 1 Immunohistochemical staining of EpCAM on TCC of the bladder. Tissue samples were formalin fixed, paraffin embedded, and mounted onto coated microscope slides. Test slides containing **A**) normal bladder, **C**) EpCAM-negative TCC, and **E**) EpCAM-positive TCC tissue sections were incubated with the primary antibody VB4-845 and VB4-845 cell surface binding detected with a secondary antibody, rabbit anti-*Pseudomonas* ETA (Sigma, catalog no. P2318, St. Louis, MO, USA). Specificity of EpCAM staining was demonstrated with the corresponding control slides, **B**) normal bladder, **D**) EpCAM-negative TCC, and **F**) EpCAM-positive TCC, treated only with the secondary antibody. Membranous staining (2+) is only apparent with the EpCAM-positive TCC tissue section **E**) incubated with both VB4-845 and the secondary antibody. All pictures are shown at 100 × magnification.

Table 2 Disease risk factors at baseline

Risk factor	Number of patients N = 64
Aggressive histology (Ta, TIS or T1 Grade 3)	39
≥2 Disease recurrences	61
Prior BCG failures ≥2 cycles	35
Last BCG failure ≤6 months	22
Disease duration >4 years	21
Number of patients with ≥1 risk factor at baseline	63/64 (98)[a]
Number of patients with ≥3 risk factors at baseline	41/64 (64)

Note: [a]Percentages are shown in parentheses.

Safety

Forty-one of the 64 patients (64%) experienced an AE during the course of the study. Twenty-one (33%) patients experienced only AEs that were assessed by the investigator as unrelated to study treatment. Classifying the AEs as unrelated to the study drug was decided after considering the temporal relationship of the onset of the event to the administration of the study drug, whether the event could be explained by concomitant medications or concurrent disease, the response to withholding the study drug, and the response to rechallenge with the study drug. These included, but were not limited to, urinary tract infection, incontinence, nocturia, pharyngolaryngeal pain, and bladder spasm. The remaining 20 patients (31%) experienced AEs judged to be related to VB4-845 administration. The most common treatment-related AEs

Table 3 Number of patients per dose cohort

Dose level (mg)	Number of patients
0.1	4
0.2	3
0.33	5
0.66	5
1.32	3
2.64	5
5.28	6
10.56	5
13.73	3[a]
17.85	7
23.20	10
30.16	8[b]
Total	64

Notes: [a]One treatment-unrelated death. This patient was not included in the assessment for efficacy; [b]Two patients had not received prior BCG treatment and were not included in the efficacy assessment.

were dysuria and hematuria (Table 4). Systemic AEs included fatigue, fever and chills, loss of appetite, myalgia, dizziness, and nausea. The frequency of treatment-related AEs did not increase with dose escalation (Figure 2). All treatment-related AEs were Grade 1 or 2, with the exception of one Grade 3 occurrence of hematuria that was reported as possibly related to VB4-845 administration. This event was not reported as a DLT as the investigator judged it to be related to aspirin use, and the patient experienced no AEs with subsequent VB4-845 dosing. There were no cases where the occurrence of AEs required discontinuation of treatment, and no patient experienced a serious AE related to the administration of VB4-845. There was one patient death due to cardiac failure, which occurred 3 weeks after the last dose of VB4-845. This death was assessed by the investigator as unrelated to study treatment and attributed to long-standing coronary artery disease, previous myocardial infarction, and hypertension.

Table 4 Adverse events related to VB4-845 administration

Adverse event	Number of patients per grade[a]		
	Grade 1	Grade 2	Grade 3
Local			
Dysuria	7	2	0
Hematuria	5	1	1
Pollakiuria	2	2	0
Micturition urgency	3	1	0
Enuresis/nocturia	2	1	0
Urinary retention/incontinence	1	2	0
Bladder spasm	2	0	0
Bladder hemorrhage	1	1	0
Instillation site abnormalities	1	0	0
Systemic			
Fatigue	5	0	0
Pyrexia/chills	2	2	0
Anorexia/decreased appetite or weight	2	2	0
Myalgia	2	1	0
Nausea/vomiting	0	2	0
Dizziness	2	0	0
Dry mouth/tongue	2	0	0
Nasopharyngitis/cough	2	0	0
Hypotension	0	1	0
Erythema/rash	1	1	0
Arthralgia	0	1	0
Headache	0	1	0
Diarrhea	0	1	0
Alopecia/abnormal hair growth	1	1	0
Pruritis	1	0	0
Dysgeusia	1	0	0
Neck pain	1	0	0
Peripheral sensory neuropathy	1	0	0

Note: [a]If a patient experienced an adverse event more than once, the event with the highest grade was tabulated.

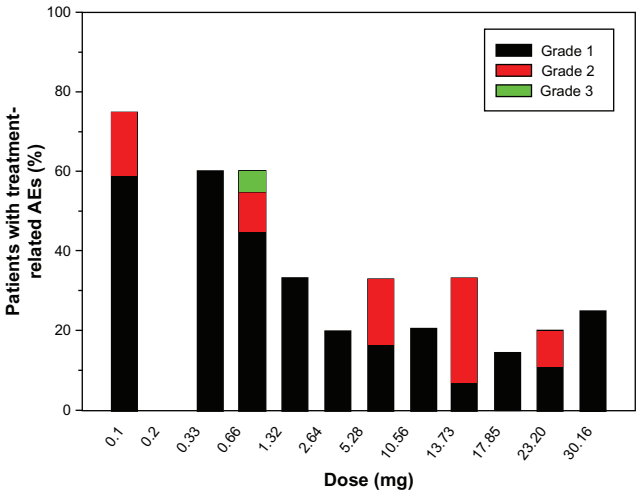

Figure 2 Percentage of patients experiencing treatment-related adverse events (AEs) by grade per dose level. Of the 41 patients experiencing AEs, 20 patients experienced AEs related to treatment. AEs at each dose level are proportioned according to the grade level. If a patient experienced an AE more than once, only the event with the highest grade was included in the calculation. The dose levels and corresponding total number of AEs are as follows: 0.01, n = 9; 0.20, n = 0; 0.33, n = 6; 0.66, n = 12; 1.32, n = 1; 2.64, n = 9; 5.28, n = 6; 10.56, n = 1; 13.73, n = 6; 17.85, n = 1; 23.20, n = 7; and 30.16, n = 2.

Pharmacokinetics

Postinstillation plasma levels of VB4-845 were measured in 63 patients, except at the final visit where samples were provided by 61 patients. In almost all patients, VB4-845 plasma levels were below the limit of detection of the assay (14 pg/mL) at all time points examined. VB4-845 was detectable in only two patients: one had levels of 19 and 17 pg/mL at 1 h after VB4-845 instillation and on day 8 prior to dosing, respectively, and the other had a level of 18 pg/mL at the 1 h time point.

Immunogenicity

The immunogenicity of VB4-845 was examined by analyzing HAPA and HAHA titers in blood samples taken at specified time points during the trial (Table 5). HAPA response was more vigorous, as patients developed a measurable titer earlier; the majority of patients exhibited HAPA by day 29, with 77% (47/61) having a measurable titer at final visit. In contrast, only 16% (10/61) of patients had HAHA by the end of the study. HAPA titers were also generally higher, with a mean maximum titer of 20,512 versus 3373 for HAHA responses. A comparison of mean titers of the HAPA and HAHA responses measured in samples taken on the final visit showed no significant difference between responders and nonresponders (data not shown). The absence of any apparent relationship between antibody titer and response to treatment suggests that the immune response was not detrimental to clinical outcome.

Table 5 Antibody responses to the ETA and scFv portions of VB4-845

Day	HAPA response			HAHA response		
	# Patients[a]	Mean titer ($\times 10^3$)	SE	# Patients[a]	Mean titer ($\times 10^3$)	SE
8	1/63	2.512	N/A	0/63	0	N/A
15	12/63	17.060	1.596	2/63	1.462	1.161
22	27/63	14.222	1.380	6/63	2.408	1.196
29	37/63	17.140	1.309	7/63	2.700	1.303
36	45/63	18.408	1.276	8/63	3.662	1.312
55	47/61	20.512	1.241	10/61	3.373	1.132

Note: [a]Number of patients with a detectable response/number of patients evaluated. Mean titer is calculated as the geometric mean of all patients with a measurable titer at the given time point.
Abbreviation: SE, standard error.

Exploratory efficacy

Sixty-one patients were considered to be evaluable for efficacy; two patients were excluded from the efficacy analysis due to an absence of BCG treatment prior to the study, and there was one study-unrelated death for whom no final tumor assessment was obtained.

Complete response based on tumor classification at baseline and dose group is summarized in Table 6. Overall, a complete response was achieved by 39% (24/61) of the patients. Of the patients with TIS, 29% achieved a complete response, while complete responses were observed in 44% and 43% of the patients with T1 and Ta, respectively. Of the five patients classified as BCG intolerant, only one (20%) had a complete response.

Given the limited number of patients per dose cohort, it was not possible to make definitive individual dose comparisons. In order to examine a potential dose response, patients were classified into three dose groups: (0.1 to <1.0 mg) = lowest dose group; (1.0 to <10.0 mg) = middle dose group; and (≥10.0 mg) = highest dose group. A comparison of the response rates in the lowest dose group versus the combined middle and highest dose group revealed a statistically significant *P*-value of 0.0418.

Table 6 Tumor response by stage and dose group

Response classification	Complete response rate
Evaluable patients	24/61 (39)[a]
Tumor stage at baseline	
TIS	5/17 (29)
T1	7/16 (44)
Ta	12/28 (43)
Dose group	
0.1 mg–<1.0 mg	3/17 (18)
1.0 mg–<10.0 mg	7/14 (50)
≥10.0 mg	14/30 (47)

Notes: [a]Percentages are shown in parentheses. *P*-value for lowest vs middle dose group = 0.1206. *P*-value for lowest vs highest dose group = 0.0622. *P*-value for lowest vs middle + highest dose groups combined = 0.0418.

Discussion

TCC is the most common cancer of the bladder, and most patients present with nonmuscle-invasive disease. Currently, BCG is the standard of care for this malignancy. Despite its well-documented therapeutic benefit, BCG therapy is delayed or discontinued in a large proportion of patients due to associated toxicity. In rare instances, patients can develop severe conditions associated with BCG infection, in some cases life-threatening, rendering BCG a nonviable treatment option. Termination of treatment due to adverse effects is not uncommon for intravesical therapies. In addition, for those patients who fail to respond to BCG therapy or experience early disease recurrence, alternative therapeutic options are limited. Given the potential for intolerance and the high rate of recurrence in patients with NMIBC, alternative treatments are under investigation.

Targeted therapies limit drug exposure to only diseased cells, thereby minimizing drug-related toxicities. We have described a Phase I study of VB4-845, an anti-EpCAM scFv–ETA, administered intravesically to high-risk patients. Of the 75 patients initially screened for participation, 74 (99%) showed EpCAM-positive disease. This high rate of EpCAM expression suggests that EpCAM represents a significant antigen for VB4-845-targeted therapy in patients with advanced NMIBC. Although not performed in this study, an examination of the expression levels of EpCAM in biopsy samples obtained from patients with residual disease following VB4-845 treatment might be informative and will be considered for future studies.

AEs experienced with VB4-845 were mild and easily managed, and no AE required the discontinuation of treatment, even in the highest dose cohort. Although the presence of pre-existing lower urinary tract symptoms may make a determination of the frequency of AEs difficult, what is evident is that the relatively mild toxicities experienced with VB4-845 are in direct contrast to other intravesical therapies where local and systemic toxicities can be treatment limiting. VB4-845 is a targeted therapy that exerts its effect via specific interaction with the cell surface antigen EpCAM. Although overexpressed on carcinoma cells, EpCAM expression is lower on normal tissue and limited to the basal layers rather than luminal surfaces. These features could minimize drug-related toxicities and may explain why related AEs were predominantly Grade 1 and 2. It is also interesting to note that failure to reach an

MTD for VB4-845 over the dose range tested and the apparent absence of any relationship between the appearance of AEs and dose are in keeping with its excellent safety profile.

Pharmacokinetic analyses indicated that VB4-845 was not systemically absorbed and remained within the bladder until elimination by voiding. This is anticipated, given the integrity of the bladder and the molecular size of VB4-845 (~69 kDa).

VB4-845 was shown to be immunogenic with the toxin portion eliciting the more vigorous response. Given the humanization of the scFv antibody fragment and entirely foreign nature of the bacterial toxin, the more intense immune response against the toxin was expected. A similar pattern of immune response was observed with LMB-2, a scFv–ETA immunotoxin, whereby more patients exhibited a stronger response to the ETA moiety than to the scFv portion.[20] Despite the observed immunogenicity, the development of an immune response was not considered to have any bearing on clinical outcome, as there was no apparent relationship between antibody titer and response to treatment. Rather, the presence of circulating antibodies to VB4-845 may, in fact, limit any systemic exposure that may occur by rapidly clearing any drug that may enter circulation. Together, the specificity of VB4-845 and its lack of systemic exposure translate to a very acceptable safety profile.

Although the Phase I trial was primarily designed to determine the MTD, tumor response was assessed as a single efficacy endpoint at 3 months to elucidate any observable trends. Although dosing was not optimized for therapeutic benefit, complete responses were observed across all tumor stages and dose groupings. Although it is not possible to draw definitive conclusions between individual dose and response to treatment, when examined according to dose groups, the data are suggestive of an increased response with higher doses. Although no direct examination of receptor occupancy has been performed, the dose range of VB4-845 administered far exceeds the drug concentration required to achieve >99% cell killing in EpCAM-positive bladder tumor cell lines. Therefore, it is possible that the tumor response may be saturated at the higher doses. It should be noted that the short duration of follow-up is a significant limitation with respect to assessing efficacy; thus, efficacy results reported in this study are considered preliminary and serve only to support further clinical trials with longer follow-up assessments.

Conclusions

Intravesical therapy with the anti-EpCAM fusion protein VB4-845, for the treatment of NMIBC was extremely well tolerated. AEs were generally mild and very manageable with no patients experiencing any serious AEs related to VB4-845 therapy. The lack of detectable postinstillation plasma levels in the vast majority of patients indicates that the drug is effectively held within the bladder and not systemically absorbed. Although most patients developed antibody titers, the data obtained in this study showed no evidence of detrimental effects on clinical outcome associated with the immune response. Preliminary efficacy results from this high-risk, often treatment-refractory, patient population suggest that VB4-845 can safely inhibit tumor growth in patients with EpCAM-positive, high-grade NMIBC. This promising finding warrants investigation in a larger clinical trial with optimized dosing.

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Disclosure

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