A Phase II Study of Oportuzumab Monatox: An Immunotoxin Therapy for Patients with Noninvasive Urothelial Carcinoma In Situ Previously Treated with Bacillus Calmette-Guérin

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Abbreviations and Acronyms

AE = adverse event
BCG = bacillus Calmette-Guérin
CIS = carcinoma in situ
CR = complete response
EOS = end of study
EpCAM = epithelial cell adhesion molecule
ITT = intent to treat
OM = oportuzumab monatox
TCC = transitional cell carcinoma
TURBT = transurethral resection of bladder tumor

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For another article on a related topic see page 1951 in this issue.

Purpose: A phase II study was performed to assess the efficacy and tolerability of intravesical oportuzumab monatox in patients with urothelial carcinoma in situ of the bladder. Bacillus Calmette-Guérin treatment had previously failed in all patients.

Materials and Methods: A total of 46 patients received 1 induction cycle of 6 (cohort 1) or 12 (cohort 2) weekly intravesical oportuzumab monatox (VB4-845) instillations of 30 mg, followed by up to 3 maintenance cycles of 3 weekly administrations every 3 months.

Results: A complete response to oportuzumab monatox was seen in 9 of 22 patients (41%) in cohort 1 and 9 of 23 (39%) in cohort 2 at the 3-month evaluation. A total of 20 patients (44%) achieved a complete response. Two other patients without carcinoma in situ who achieved a complete response were not included in the study due to the development of noninvasive papillary (Ta) disease. Median time to recurrence in patients who achieved a complete response was 274 and 408 days in cohorts 1 and 2, respectively. Overall 7 patients (16%) remained disease-free. Post-study assessment demonstrated that these patients were still disease-free at last followup (18 to 25 months). The most common adverse events were mild to moderate reversible bladder symptoms.

Conclusions: Oportuzumab monatox was effective and well tolerated in patients with bacillus Calmette-Guérin refractory carcinoma in situ of the bladder. These results demonstrate the clinical benefit of oportuzumab monatox and support its continued development for the second line treatment of nonmuscle invasive bladder cancer.

Key Words: immunotoxins; carcinoma in situ; urinary bladder; administration, intravesical; clinical trials, phase II

MOST patients with bladder cancer (more than 90%) have urothelial or transitional cell carcinoma.[1] Approximately 70% of cases are noninvasive (stages CIS, Ta [papillary tumor] or T1), while the remaining cases are muscle invasive or nodal disease.[2,3] Approximately 10% of all patients with noninvasive bladder cancer have CIS.[4,5]

Primary therapy for CIS depends on whether another concurrent stage of bladder cancer is diagnosed. TURBT is recommended to remove Ta or T1 tumors before adjuvant intravesical therapy with chemotherapy and/or BCG to treat CIS.[1,6] In the absence of Ta or T1 disease, BCG is the usual first line therapy for patients with

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CIS.[1,2] Although there are alternative intravesical therapies for patients in whom BCG fails and who are medically unfit or wish to delay cystectomy, cystectomy is usually recommended in the event of relapse.[1] There is an unmet medical need for bladder sparing treatments after BCG or other intravesical treatment failure.

Oportuzumab monatox, also known as VB4-845, is a recombinant fusion protein comprising a humanized anti-EpCAM single-chain antibody linked to Pseudomonas exotoxin A (ETA(252-608)).[7] Once bound to the cancer cell, OM is internalized and the toxin moiety released into the cytosol where it induces apoptosis.[8] OM has been developed for locoregional delivery. Intravesical administration limits systemic exposure while maximizing local drug concentration, thereby increasing the therapeutic window. Earlier clinical results in patients with noninvasive TCC of the bladder indicated that OM was well tolerated and showed preliminary efficacy with an indication of a dose-response effect.[9]

We report the efficacy, safety and tolerability of 2 OM dosing strategies in patients with urothelial CIS in whom BCG previously failed. It is hypothesized that the response rate measured for OM will be sufficient to warrant further investigation as well as provide insight regarding the preferred dosing regimen.

MATERIALS AND METHODS

Study Population

Patients were enrolled at 21 sites in North America (March 2007 to July 2008). Patients 18 years old or older with histologically confirmed TCC of the bladder and residual CIS, with or without concurrent Ta or T1 tumors, who were refractory/intolerant to 1 or more cycles of BCG in the 24 months before enrollment and whose tumor was EpCAM positive, were eligible for study inclusion. Cases were considered BCG refractory if they did not achieve disease-free status or had recurrence within 6 months of the last BCG treatment cycle, and considered BCG intolerant if BCG side effects prevented them from completing therapy.[10,11] Other study inclusion criteria were more than 12-month life expectancy with normal renal and hepatic function. The study was conducted in compliance with institutional review board/independent ethics committees, informed consent regulations, the International Committee on Harmonisation Good Clinical Practice Guidelines, the Declaration of Helsinki and local regulations pertaining to the use of new therapeutic agents.

Study Design

An open label, multicenter, 2-arm trial (NCT00462488) using a single stage design was used to assess and compare the efficacy and tolerability of 2 OM intravesical treatment schedules lasting up to 1 year. At each administration 30 mg OM in 40 ml sterile phosphate buffered saline was instilled into the bladder via catheter, retained for 2 hours and then voided. The dosing regimen was based on a previous phase I/II dose escalation study consisting of an initial induction cycle, followed by maintenance cycles of 3 weekly instillations and then 9 weeks of no therapy (fig. 1).[9] In cohort 1, 23 patients received an induction cycle that consisted of 6 weekly instillations. At the 3-month assessment patients with persistent CIS but no disease progression, ie T2 or less, were eligible for maintenance dosing or repeat of the induction cycle as per protocol. Cohort 2 was added to the protocol to achieve increased exposure to OM during the induction cycle. In cohort 2, 23 patients received 12 weekly instillations fol-

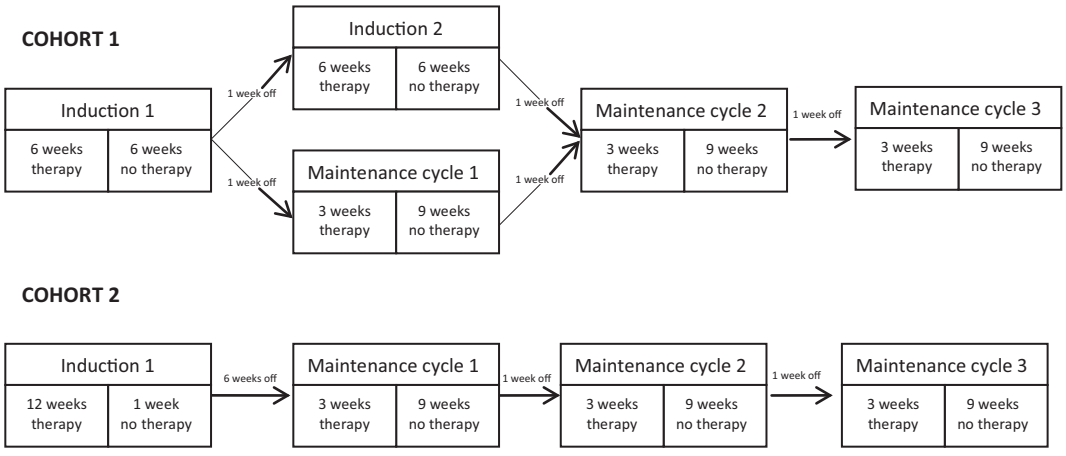

Figure 1. Treatment schedule diagram. Patients in cohort 1 were divided between 2 protocol versions. Most patients in cohort 1 (19) were treated under protocol 1.1, in which those who had residual disease at 3 months but no progression could go on to maintenance cycle. Only 7 of 11 patients with residual disease eligible for maintenance cycle did go on to maintenance, and remaining 4 patients were removed from trial. In cohort 1, 3 patients were treated under protocol 2.0, in which those with residual disease at 3 months could receive second 6-week induction. Of these patients 2 received second induction course but did not achieve CR. After induction cycle in cohort 2 patients continued on to first maintenance cycle only if there was no evidence of disease. Assessments were conducted at weeks 12, 25, 38 and 51 for cohort 1, and at weeks 13, 31, 44 and 57 for cohort 2.

lowed by 6 weeks of no therapy and then maintenance dosing as described for cohort 1. Patients discontinued treatment if they exhibited persistent or progressive disease after induction treatment for cohort 2 and after first maintenance treatment for cohort 1.

Patient Evaluation

Pretreatment screening and baseline evaluations included physical examination, medical history and cystoscopy with directed and random mapping biopsy of suspicious as well as normal appearing areas for possible CIS. TURBT was performed for Ta and T1 tumors but T1 re-resection was not mandated by protocol and was left to clinician discretion. The absence of upper tract disease was confirmed by imaging. Hematology and clinical chemistry analyses were performed before treatment as well as at each scheduled posttreatment evaluation. Laboratory and histological assessments were all performed locally by accredited and certified laboratories.

Immunohistochemistry for EpCAM expression was performed on the index tumor at a central laboratory.[9] Biopsied material was incubated with OM and binding detected with rabbit anti-Pseudomonas ETA (Sigma). Slides were examined by a pathologist, and staining intensity scored as 0 to 3+ (0—negative, 1+ —weak, 2+—moderate, 3+—strong). EpCAM expression was defined as any membranous staining above background, whether or not completely circumferential. The percentage of cells exhibiting membrane staining was also evaluated. All patient biopsies were determined to be EpCAM positive, with more than 95% scoring 2 to 3+, with 15% to 100% cells stained (data not shown).

Efficacy parameters were monitored at the end of each induction and maintenance cycle as well as at the end of study. Tumor response was evaluated using standard cystoscopy to document tumor location and quantify the overall area of affected bladder. Urine cytology with random biopsies from at least 2 areas of normal appearing urothelium and directed biopsies of any suspicious area or of apparent persistent disease were also assessed. A complete response was defined as no histological evidence of disease and negative urine cytology at the 3-monthly evaluations. Any cases with no histological evidence of disease on initial biopsy but atypical or suspicious urine cytology were also considered CRs only if they remained negative after being evaluated with repeat biopsy, directed and random. Censoring rules were applied to the estimation of the distribution of time to event end points and other analyses excluded subjects with missing values.

A Fleming 1-sided exact proportions test was used in each cohort to test the null hypothesis that the CR rate was 5% or less (considered unacceptable) vs the alternative hypothesis of 25% or greater CR (warranting further development).[12] Assuming a type I error of 5% and a power of 80%, a minimum of 21 patients was required in each cohort. A between-group difference in CR rates of more than 15% would be detected with an 80% probability, using the indifference zone approach.[13] SAS® version 9.1 was used for the statistical analysis.

Safety was evaluated by monitoring AEs, laboratory results and performing regular physical examinations. All treatment emergent bladder symptoms were reported as adverse events. AEs were judged to be treatment related by the investigators if they were considered possibly, probably or definitely related to OM.

RESULTS

Patient Characteristics

A total of 46 patients with CIS and a median age of 74 years (range 41 to 92) were enrolled into 1 of the 2 treatment cohorts (table 1). At screening TURBT was performed in 11 and 8 patients with concurrent Ta and T1 tumors, respectively. All patients had previously received 1 to 8 cycles of BCG (a cycle was defined as instillation once a week for 6 consecutive weeks) with a mean of 2.15 (±1.7) cycles. Almost all patients did not achieve a CR by the last BCG treatment (82%) (table 2). Two patients who initially achieved a CR after the last BCG treatment experienced disease recurrence before enrollment at 4 and 18 months after treatment, respectively. All but 1 patient who had recurrence after 18 months met the definition of BCG refractory. Of 6 patients recorded as BCG intolerant, 3 were also considered BCG refractory.

One patient in cohort 1 who received only 1 instillation of OM was removed from the study after receiving an investigational drug during the wash-

Table 1. *Patient characteristics*

	Cohort 1	Cohort 2	Overall
No. pts	22	23	45
Age:			
Mean (SD)	71.6 (12.60)	71.5 (9.34)	71.6 (10.93)
Median	75.0	72.0	74.0
Range	41.0–89.0	54.0–92.0	41.0–92.0
No. age category (%):*			
Younger than 65	5 (22.7)	4 (17.4)	9 (20.0)
65 or Older	17 (77.3)	19 (82.6)	36 (80.0)
75 or Older	13 (59.1)	9 (39.1)	22 (48.9)
No. gender (%):			
M	16 (72.7)	19 (82.6)	35 (77.8)
F	6 (27.3)	4 (17.4)	10 (22.2)
No. ethnicity (%):			
Hispanic or Latino	1 (4.5)	0	1 (2.2)
Not Hispanic or Latino	21 (95.5)	23 (100.0)	44 (97.8)
No. race (%):			
Black, African-American or of African Heritage	0	1 (4.3)	1 (2.2)
White	21 (95.5)	22 (95.7)	43 (95.6)
Other	1 (4.5)	0	1 (2.2)
Yrs since initial bladder Ca diagnosis:			
Mean (SD)	3.3 (3.64)	5.1 (5.97)	4.2 (5.00)
Median	1.8	2.8	2.3
Range	0.4–14.3	0.6–23.3	0.4–23.3
No. disease stage (%):			
CIS+Ta	4 (18.2)	7 (30.4)	11 (24.4)
CIS	13 (59.1)	13 (56.5)	26 (57.8)
CIS+T1	5 (22.7)	3 (13.0)	8 (17.8)

* Categories are not mutually exclusive.

Table 2. *Previous BCG treatment for bladder cancer*

	No. Cohort 1 (%)	No. Cohort 2 (%)	Total No. (%)
No. pts	22	23	45
Complete response	0	2 (8.7)	2 (4.4)
Failed to respond	17 (77.3)	15 (65.2)	32 (71.1)
Partial response*	3 (13.6)	2 (8.7)	5 (11.1)
Intolerant	2 (9.1)	4 (17.4)	6 (13.3)

BCG response pertains to most recent treatment received.
* Defined as negative biopsies following therapy but with persistent positive cytology.

out period. Two other patients in cohort 1, despite having no progression of CIS, were withdrawn from the study at 3 months while a third withdrew consent. The remaining 42 patients completed the treatment regimens according to protocol (fig. 2).

Efficacy

CR rates in the ITT population are shown in table 3. Of evaluable patients treated with OM 44% (20 of 45) achieved a CR. The percentage of patients who achieved a CR at the 3-month evaluation was similar between cohorts 1 and 2 at 41% (9 of 22) and 39% (9 of 23), respectively. A response rate of more than 25% was maintained in both cohorts at the 6-month point but decreased below the 25% level at 9 months. A durable CR was evident in 16% of patients who were still disease-free at the 1-year EOS assessment. In almost all cases CR was achieved by 3 months after administration of a single induction course (6 weeks for cohort 1 or 12 weeks for cohort 2). Interestingly, 2 patients in cohort 1, with persistent CIS at week 12 after a single induction treatment, achieved a CR after the administration of the first 3-week maintenance course of OM as allowed per protocol in cohort 1. In addition, 1 patient in each cohort remained free of CIS but had low grade (grade less than 2) papillary tumor(s) develop. These patients were considered nonresponders and were discontinued from the study as required per protocol. Only 2 patients (1 in cohort 1 at 6 months and 1 in cohort 2 at 3 months) experienced disease progression during followup. Both patients had progression to pathological stage T2 disease, and 1 may have had disease under staged at enrollment.

Durable responses were evident in heavily and less heavily treated patients (table 4). On the whole the 1-year recurrence rate for CRs was 65% (13 of 20). Of the 11 patients with CR at any point in cohort 1, 8 experienced recurrence of CIS by the EOS assessment with a median time to recurrence from the first dose date of 274 days. In contrast, only 5 of the 9 patients in cohort 2 (55.5%) with CR experienced recurrence before the 12-month assessment. Overall median time to recurrence from the first dose date in cohort 2 was 408 days. While no statistically significant difference was observed between the 2 dosing strategies (log rank test $p = 0.1708$, fig. 3), the distinct separation between the 2 dose cohorts beyond 150 days suggests a trend to an increase in time to recurrence associated with cohort 2.

Limited long-term followup for patients free of disease after study completion was available. Of the 3 patients with CR in cohort 1 who reached EOS, 2 remained CIS-free for at least 18 months. The third patient was free of disease for approximately 2 years after the first dose. This patient subsequently underwent cystectomy, thereby achieving bladder preservation for approximately 2 years. The 4 patients with CR in cohort 2 who reached EOS remained free of disease for at least 18, 21, 23 and 25 months, respectively.

Although the time to cystectomy was not recorded, informal followup for 8 patients revealed a median time to cystectomy of 3 months, with high grade, noninvasive disease (Tis in 4, Ta in 3, T1 in 1). Based on the pathology and a recommended followup monitoring period of 3 months, patients were not considered at risk by study participation.[1]

Safety

A total of 43 patients (93.5%) reported at least 1 treatment emergent AE during the course of the study. The most common events were dysuria, hematuria, pollakiuria, urgency, nocturia and bladder pain. There were 30 patients (65%) who reported

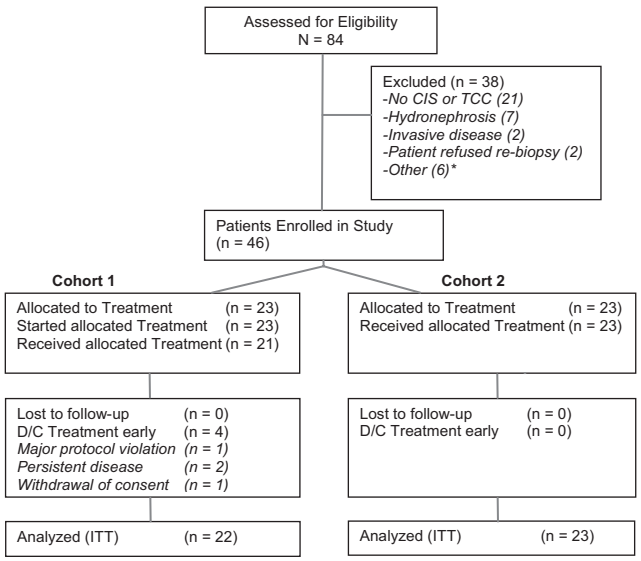

Figure 2. CONSORT diagram. Exclusion criteria were urethral or upper tract TCC, hydronephrosis and any chemotherapy (systemic, intravesical or investigative inclusive of single dose adjuvant intravesical chemotherapy immediately after TURBT) in prior 2 months. Asterisk indicates others excluded for creatinine clearance (1), upper tract disease (1), prostatic urethral tissue involvement (1), enrollment complete (1), prostate cancer (1) and inadequate renal function (1). *D/C*, discontinued.

Table 3. *CR rates in ITT population*

	No./Total No. (%, 95% CI)		
	Cohort 1	Cohort 2	Totals
At any point*	11/22 (50.0, 28.2–71.8)	9/23 (39.1, 19.7–61.5)	20/45 (44.4, 29.6–60.0)
At 3 mos	9/22 (40.9, 20.7–63.6)	9/23 (39.1, 19.7–61.5)	18/45 (40.0, 25.7–55.7)
At 6 mos	6/22 (27.3, 10.7–50.2)	6/23 (26.1, 10.2–48.4)	12/45 (26.7, 14.6–41.9)
At 9 mos	3/22 (13.6, 2.9–34.9)	5/23 (21.7, 7.5–43.7)	8/45 (17.8, 8.0–32.1)
At 12 mos	3/22 (13.6, 2.9–34.9)	4/23 (17.4, 5.0–38.8)	7/45 (15.6, 6.5–29.5)

* Refers to the total number of CRs at the 3-month assessment plus any additional CRs following maintenance or a second induction course as allowed per protocol in cohort 1. Note that in addition to the 9 CRs at the 3-month assessment in cohort 1, 2 other patients in cohort 1 who had evidence of disease at 3 months later achieved CR following 1 maintenance cycle.

AEs related to OM treatment, the majority being local bladder symptoms (table 5). Types and distribution of AEs were comparable between the treatment schedules. Treatment related AEs were mild or moderate in severity except 3 severe events, all of which were resolved without sequelae. Renal and urinary treatment related AEs were reported by the majority of patients (80%) at baseline. No patient discontinued treatment due to an AE, reported a serious AE that was related to OM or died during the study.

Table 4. *Description of OM complete responders*

	OM Treatment		
Prior Intravesical Therapies*	Tumor Staging at Baseline	Tumor Staging at Last Visit	Days to Failure or Last Followup†
Cohort 1:			
BCG	CIS	CIS	145
BCG	CIS	CIS	153
BCG	CIS	T2	172
BCG × 4, mitomycin C	CIS	CIS	175
BCG, mitomycin C	CIS/TaG2	TaG1	187
BCG	CIS	CIS	269
BCG × 2	CIS	CIS	274
BCG	CIS	CIS/TaG3	281
BCG‡	CIS	CR	356
BCG × 2‡	CIS/TaG3	CR	356
BCG × 2‡	CIS	CR	370
Cohort 2:			
BCG × 2	CIS	T1G3	208
BCG × 2	CIS	CIS	209
BCG × 2, interferon	CIS	CIS	230
BCG × 8	CIS	CR	391
BCG	CIS	CIS	393
BCG × 4, interferon, mitomycin C§	CIS	CR	393
BCG × 6§	CIS	CIS	408
BCG × 2, interferon, thiotepa§	CIS	CR	412
BCG, interferon§	CIS	CR	428

* Only responders at any time point are included.
† Time from first dose to the date of first disease recurrence or end of study evaluation.
‡ Two of these 3 patients from cohort 1 showed no recurrence for more than 18 months, and 1 remained free of disease for 2 years and subsequently underwent cystectomy.
§ These 4 patients were free of disease at 18, 21, 23 and 25 months.

DISCUSSION

CIS is the most aggressive stage of nonmuscle invasive bladder cancer and is often refractory to currently available treatment. Radical cystectomy is recommended due to the risk of progression to invasive disease. While cystectomy has the highest cure rate, not all patients are candidates. Moreover complications and associated comorbidities can dramatically impact quality of life.[14,15] Therefore, patients and urologists often view cystectomy as a last resort therapeutic intervention.[16] Given the limited therapeutic options for these patients, OM represents a potential bladder sparing treatment that addresses an unmet medical need.

OM was well tolerated in both cohorts as all patients completed treatment on schedule. This unique level of tolerability associated with OM's targeted approach contrasts strongly with nonspecific intravesical therapies based on immune modifiers such as BCG or chemotherapy, which patients may discontinue due to drug intolerability or subsequent treatment associated, secondary complications.[17–19]

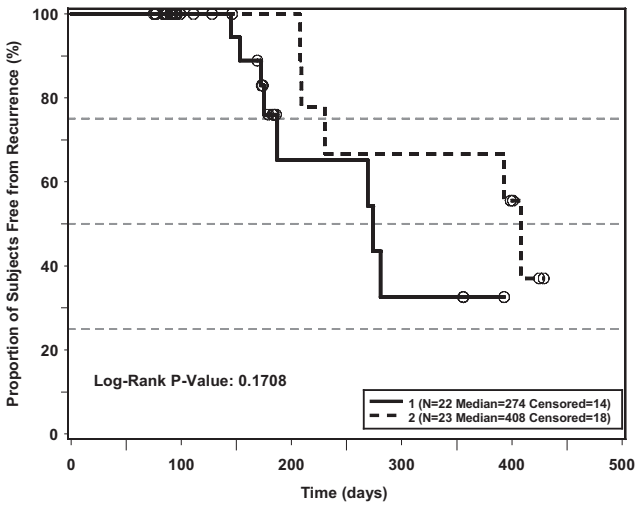

Figure 3. Time to recurrence, Kaplan-Meier plot of ITT population. Circles indicate censored patients.

Table 5. *Subject incidence of treatment related adverse events*

	Intensity	No. Cohort 1 (%)	No. Cohort 2 (%)	Total No. (%)
No. pts		23	23	46
No. pts with at least 1 AE		13 (56.5)	17 (73.9)	30 (65.2)
Gastrointestinal disorders	Mild	1 (4.3)	2 (8.7)	3 (6.5)
General disorders + administrative site conditions*	Mild–moderate	9 (39.1)	3 (13.0)	12 (26.1)
Infections + Infestations†	Mild–moderate	1 (4.3)	4 (17.4)	5 (10.9)
Investigations‡	Mild–moderate	1 (4.3)	2 (8.7)	3 (6.5)
Nervous system disorders§	Mild–moderate	2 (8.7)	1 (4.3)	3 (6.5)
Renal + urinary disorders		12 (52.2)	17 (73.9)	29 (63.0)
Bladder discomfort	Mild	1 (4.3)	0 (0.0)	1 (2.2)
Bladder pain	Mild	3 (13.0)	1 (4.3)	4 (8.7)
Bladder spasm	Mild	1 (4.3)	1 (4.3)	2 (4.3)
Dysuria:				
Mild		4 (17.4)	10 (43.5)	14 (30.4)
Moderate		4 (17.4)	4 (17.4)	8 (17.4)
Severe		0 (0.0)	1 (4.3)	1 (2.2)
Hematuria:				
Mild		3 (13.0)	1 (4.3)	4 (8.7)
Moderate		1 (4.3)	1 (4.3)	2 (4.3)
Hemorrhage urinary tract	Mild	2 (8.8)	1 (4.3)	3 (6.5)
Incontinence	Mild	1 (4.3)	0 (0.0)	1 (2.2)
Micturition urgency:				
Mild		1 (4.3)	3 (13.0)	4 (8.7)
Moderate		1 (4.3)	1 (4.3)	2 (4.3)
Nocturia:				
Mild		0 (0.0)	1 (4.3)	1 (2.2)
Moderate		1 (4.3)	2 (8.7)	3 (6.5)
Pollakiuria:				
Mild		1 (4.3)	3 (13.0)	4 (8.7)
Moderate		0 (0.0)	2 (8.7)	2 (4.3)
Severe		1 (4.3)	1 (4.3)	2 (4.3)
Urge incontinence	Mild	1 (4.3)	0 (0.0)	1 (2.2)
Urinary incontinence:				
Mild		1 (4.3)	1 (4.3)	2 (4.3)
Moderate		0 (0.0)	1 (4.3)	1 (2.2)
Urinary retention	Mild	1 (4.3)	0 (0.0)	1 (2.2)

AEs were graded using National Cancer Institute-Common Terminology Criteria for Adverse Events version 3.0 and reported using MeDRA® version 8.0. Only those System Organ Class categories in which an event is recorded in more than 5% of the patients are reported in the table.

* Administrative site conditions included asthenia, catheter site related reaction and fatigue.

† Infections and infestations included herpes zoster, nasopharyngitis and urinary tract infection.

‡ Investigations included blood urine present, cells in urine and abnormal liver function test.

§ Nervous disorders included dizziness and somnolence.

The safety profile of OM was comparable between cohorts. Similarly, initial CR rates at 3 months and the sustained CR at 1 year were not significantly different between treatment schedules. However, the median time to recurrence was 134 days longer in cohort 2. In addition, 2 patients in cohort 1 who were CIS positive 3 months later achieved CR with subsequent maintenance dosing. Albeit anecdotal, together these data suggest that a more intensive dosing schedule may translate to better CR rates and response sustainability, thus representing an area for further investigation.

The OM complete response rate at 6 months was 27% with 16% maintaining a disease-free status beyond 1 year. In comparison, valrubicin produced a sustained response at 6 months of only 21% with a median time to failure of 18 months or more. At the end of the followup evaluations only 8% of the patients on valrubicin were disease-free at a mean of 30 months.[17] A more durable response was also noted for patients on OM compared to those with high grade TCC treated with intravesical gemcitabine of whom only 10% achieved 1-year recurrence-free survival.[20] It is noteworthy that the more durable response rate for OM was achieved entirely in patients with CIS whereas only 77% of the patients on gemcitabine had CIS. In addition to the encouraging comparison to other third line intravesical treatments, the 27% response rate at 6 months for patients receiving OM also contrasts favorably with the 15% obtained with second line BCG treatment for residual disease.[2]

The response rates reported here may be conservative assessments of the potential clinical benefit of

OM. Some patients treated with OM were free of CIS but lower grade (less than 2) papillary tumor(s) developed which were manageable with local therapy. It has been suggested that such changes in disease condition constitute a sufficiently significant clinical benefit in the case that it could be considered a responder, albeit not complete.[15] Likewise, re-resection of T1 tumors at baseline would allow better staging and the exclusion of unrecognized muscle invasive disease.

CONCLUSIONS

Overall, OM provides a clinically meaningful benefit with a highly favorable safety profile in patients with BCG refractory CIS. On the basis of these results, further clinical development exploring a more frequent dosing regimen during the induction phase is planned for second and third line BCG refractory CIS cases. In addition to its use as a monotherapy, OM's unique targeted mode of action may also prove valuable combined with other intravesical therapies.

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