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## Safety, Tolerability, and Long-Term Clinical Outcomes of an IL-15 analogue (N-803) Admixed with Bacillus Calmette-Guérin (BCG) for the Treatment of Bladder Cancer

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### ABSTRACT

Intravesical BCG is active against non-muscle invasive bladder cancer (NMIBC), but bladder cancer will recur and even progress in a significant number of patients. To improve the response rate, N-803, an IL-15 superagonist was administered in combination with BCG. To evaluate the safety and efficacy associated with the use of intravesical N-803 and BCG in patients with BCG-naïve NMIBC. This phase 1b clinical trial used a 3 + 3 dose-escalation design. Participants were enrolled from July 2014 and July 2015, with follow-up and analyses through January 15, 2021. Eligibility criteria included histologically confirmed non-muscle invasive urothelial carcinoma of intermediate or high risk who had not received prior treatment with intravesical BCG (ie, BCG-naïve). All 9 participants met the eligibility criteria, received treatment according to the protocol, and were included in all analyses. Treatment was done once weekly for 6 consecutive weeks with bladder infusion of the standard dose of BCG, 50 mg/institution, in combination with increasing doses of N-803 (100, 200, or 400 µg N-803 per institution). No DLTs were noted in any of the dose cohorts. All adverse events (AEs) were manageable and less than grade 3. During the 2-year follow-up, all 9 participants were disease free. Furthermore, 6 y after treatment, all 9 participants (100%) were disease free with no evidence of disease progression and an intact bladder. This phase 1b trial found the combination of intravesical N-803 and BCG to be associated with modest toxic effects, low immunogenicity, and substantial prolonged antitumoral activity; phase 2 trials are in progress.

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### KEYWORDS

Non-muscle invasive bladder cancer; IL15; BCG



### Introduction


Bladder cancer is the sixth most common cancer in the US with more than 83,730 new cases and over 19,450 disease-related deaths expected in 2021. It is currently the fourth most commonly diagnosed solid cancer in males and the eleventh most common cancer in women with increasing incidence.<sup>1</sup> Approximately 75%–85% of bladder cancer is detected in its early stage, and is categorized as non-muscle invasive bladder cancer (NMIBC).<sup>2</sup> Treatment of NMIBC is typically aimed at reducing disease recurrence or progression to a more advanced stage. Despite the prevalence of NMIBC, treatment has seen limited advancement over the last 20 y. Intermediate and high-risk NMIBC is treated by endoscopic tumor resection, followed by intravesical chemotherapy and/or immunotherapy. Immunotherapy usually consists of intravesical administration of bacillus Calmette-Guérin (BCG), a live attenuated bacterium.<sup>3–5</sup>

The immune-mediated mechanism of action of BCG has been extensively studied. Research suggests that BCG binds selectively to the cell and is internalized resulting in a nonspecific immune response and subsequent tumor clearance through the activation of natural killer (NK) cells and CD8 + T cells.<sup>6</sup> However, as many as 70% of the patients experience either treatment failure or suffer a disease

recurrence within 5 y. Of these, 30% eventually die of bladder cancer and 50% undergo radical cystectomy.<sup>7,8</sup> Radical cystectomy is the main treatment that is offered to patients when intravesical BCG treatment has failed. Thus, novel therapies are desperately needed to reduce recurrence rates, prevent disease progression, and preserve the bladder to improve the quality of life of patients with intermediate and high-risk NMIBC. Supplementation of BCG therapy with an immune agonist that enhances the proliferation and infiltration of NK and CD8 + T cells may improve BCG-mediated tumor clearance.

N-803 (nogapendekin alfa inbakicept) is a soluble complex consisting of two protein subunits of a human interleukin (IL)-15 variant (nogapendekin alfa) bound with high affinity to a dimeric human IL-15 receptor  $\alpha$  (IL-15 R $\alpha$ ) sushi domain/human IgG1 Fc fusion protein (inbakicept).<sup>9,10</sup> This fusion protein has been designed to simulate the normal mechanism of action of IL-15 where IL-15 and IL-15 R $\alpha$  are coordinately expressed by antigen-presenting cells (monocytes and dendritic cells) and presented in trans to neighboring NK cells or CD8 + T cells expressing the CD122/CD132 receptor complex (Huntington 2009, Mortier 2006).<sup>11,12</sup> The IL-15 variant of N-803 has an asparagine (Asn) to aspartate (Asp) mutation at amino acid 72 (N72D) to further increase biological activity

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 Supplemental data for this article can be accessed on the [publisher's website](#).

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and agonism of the CD122/CD132 receptor complex resulting in increased proliferation and activation of NK cells and CD8 + T cells. In a preclinical bladder cancer model, intravesical administration of N-803 in combination with BCG reduced tumor burden and significantly increased infiltration of stimulated CD8 + T cells and NK cells in the bladder.<sup>13</sup> A phase 1b, multicenter, open-label, dose-escalation study of intravesical N-803 in combination with BCG was conducted to explore the safety and efficacy of the combination in patients with BCG-naïve NMIBC.

## Materials and methods

### Patients

Eligible patients were at least 18 y of age with histologically confirmed non-muscle invasive urothelial carcinoma of intermediate or high risk who had not received prior treatment with BCG (ie, BCG-naïve) (Figure 1), NCT02138734. High-risk disease was defined as any high-grade Ta or T1, or carcinoma in situ (CIS). Patients must have had a transurethral resection of bladder tumor (TURBT) and diagnostic biopsy within 3 months and a cystoscopy within 4 weeks prior to the start of experimental treatment. Participants with papillary disease (Ta/T1) had all visible disease resected endoscopically prior to study entry. Participants with CIS only disease could have, but were not required to have, undergone TURBT or fulguration prior to study entry. No participants had tumor lymph node invasion or metastases. Patients had an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1, and adequate organ and hematologic functions. Key exclusion

criteria were muscle-invasive or metastatic disease, lymph node involvement, and previous BCG treatment; however, one immediate postoperative adjuvant intravesical instillation of chemotherapy, gemcitabine, was permitted. It was recommended that subjects in this phase 1 study with CIS undergo biopsy to assess response and receive maintenance of intravesical BCG, but it was not mandatory (Note – For the subsequent phase 2 studies, these criteria were mandatory). The study protocol was reviewed and approved by the institutional review boards of each participating center. Informed written consent for this trial was obtained from patients according to the rules of the participating centers Institutional Review Board.

### Study design and interventions

This was a phase 1b open-label dose-escalation trial conducted at two centers in the US. A modified 3 + 3 design was used for the dose-escalation phase. Participants were sequentially enrolled into increasing N-803 dose cohorts and monitored for dose-limiting toxicities (DLTs). All participants in each cohort were administered the standard dose of BCG, 50 mg/instillation (TICE® BCG, Merck), in combination with increasing doses of N-803 (100, 200, or 400 µg N-803 per instillation). A total of 9 participants, 3 per cohort, were enrolled. N-803 and BCG were admixed and administered via a urinary catheter in the bladder weekly for 6 consecutive weeks unless unacceptable toxicity or disease progression occurred. If limited toxicities and no disease progression, then treating physicians and participants were encouraged to receive 3 weekly maintenance

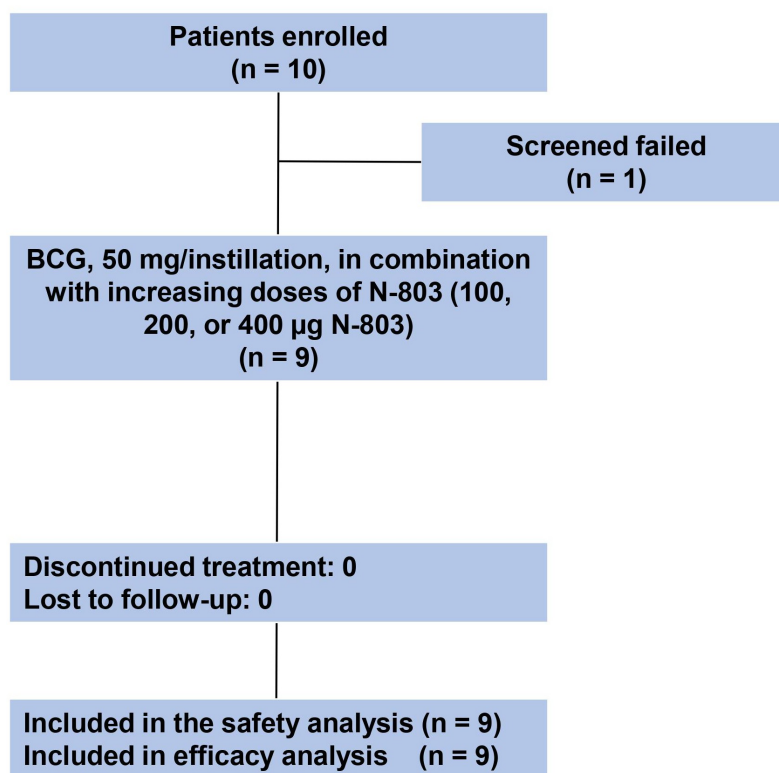


Figure 1. Study flow diagram.

instillations of BCG alone every 3 months up to 12 months and then every 6 months up to 36 months.<sup>14</sup>

Dose escalation to the next cohort was permitted if none of 3 participants experienced a study treatment-related DLT. If one subject developed a treatment related DLT, up to 6 participants were to be enrolled at that dose level and each subsequent higher dose level. If 2 or more of 3–6 participants in a dose-escalation cohort had a treatment-related DLT that dose level was designated as exceeding the maximum tolerated dose (MTD). If 3 participants had been enrolled in the previous dose level, then additional participants (up to 6 total) were to be enrolled at that dose level. If 0 or 1 out of 6 participants experienced a DLT at a specific dose level, that dose was defined as the MTD.

### **End points and assessments**

The primary end points were the safety and tolerability of N-803 in combination with BCG, the maximum tolerated dose (MTD) and recommended phase 2 dose (RP2D) of N-803, and the disease response rate. Secondary end points were immunogenicity and pharmacokinetics of N-803. All treated participants had two response assessments: an initial assessment at week 12 ( $\pm 1$  week) and a confirmatory assessment at week 24 ( $\pm 1$  week) from the start of study treatment. For each response assessment, a cystoscopy and urine cytology or fluorescence in situ hybridization (FISH) test was performed to evaluate the response. If a mass or abnormality was observed on cystoscopy, or cytology was noted to be suspicious or malignant, then an endoscopic tumor resection/bladder biopsy was performed.

Safety was evaluated by the incidence and severity of adverse events (AEs), vital signs, and clinical laboratory tests for biochemistry and hematology of all treated participants. All AEs were graded using the National Cancer Institute (NCI) Common Terminology Criteria for AEs version 4.0 (CTCAEv4.0). Treatment-related adverse events (TRAEs) were defined as any AE that began or worsened in grade after the start of study drug until 30 d after the last dose of study drug.

### **Pharmacokinetics**

Blood samples for pharmacokinetic (PK) analysis of serum levels of N-803 were collected for all enrolled participants on study day 1 immediately prior to the start of instillation, and at 30 minutes, 2 hours, 4 hours, and 24 hours after the start of the instillation.

### **Measures of interest**

Urine and serum samples were collected for all enrolled participants on study day 1 immediately prior to the start of instillation, and 4 hours after the start of instillation for biomarker analysis of the following cytokines: interleukin (IL)-2, IL-4, IL-6, IL-10, interferon (IFN)- $\gamma$ , and tumor necrosis factor (TNF)- $\alpha$ . Samples were also collected before instillation start on study days 15, 29, and 36. Cytokines were measured by commercially available antibody-based immunoassays (Corplex™ Cytokine Panel, Cat # 85–0329, Quanterix Corp, Billerica, MA).

For molecular response assessments, bladder tissue was collected at the time of study enrollment and at the week 12 and week 24 assessment visits if a mass or abnormality was noted. Tissue specimens from pre-study TURBT/biopsy were analyzed by immunohistochemical staining for the following immune cells: CD3+, CD4+, CD8+ and CD56 + .

## **Results**

### **Patient characteristics**

Between July 2014 and July 2015, nine patients were enrolled and included in the safety and efficacy analyses. The baseline characteristics of the patients are presented in Table 1. Most participants were Asian (67%), male (89%) with a median age of 65 y (range, 43–78 y). All enrolled participants had NMIBC urothelial carcinoma high risk that was confirmed by biopsy prior to study entry. At the time of study entry, seven participants had papillary disease (two Ta and five T1) and two participants had CIS. Most patients (five of nine [56%]) had only one tumor present at baseline; however, there were also three patients with two tumors, and one patient with three tumors. The longest tumor diameter measured a median of 2.0 cm (range, 1–5 cm) in one dimension. All participants were enrolled within 0.58 months of their most recent cystoscopy and within 1.6 months of their last TURBT procedure. Despite extensive counseling, only two participants (#4 and #7) went on to have prescribed maintenance BCG therapy.

### **Safety**

Adverse events and serious AEs (SAEs) are detailed in Table 2. There were no DLTs observed in any patients, thus the N-803 MTD was not reached. Overall, 9 of 9 (100%) patients experienced at least one TRAE and 7 of 9 (78%) experienced at least 1 treatment-related AE. The most common TRAE was hypertension, which occurred in 6 out of 9 (67%) patients. Other commonly observed TRAEs were hematuria, urinary frequency, and fatigue, each of which was reported in 3 out of 9 (33%) participants. All incidents of hematuria and frequency that were treatment emergent were also considered to be treatment related, whereas only two incidents (22%) of hypertension, both grade 2, were treatment related. Most AEs were either grade 1 or 2; a few were grade 3. Grade 3 AEs included 5 incidents of hypertension, none of which were considered to be treatment related, and 1 incident of treatment-related hematuria. There were no grade 4 or 5 AEs, SAEs, or DLTs. Only one subject had a delay (7 d) in the weekly treatment due to a urinary tract infection, which was treated with oral antibiotics. In addition, no AEs led to the discontinuation of the study drug and there were no deaths associated with study drug administration. There was no observed dose-dependence in the frequency or seriousness of the AEs, and overall the combination of N-803 plus BCG was well tolerated.

### **Pharmacokinetics**

N-803 was detected in serum samples from 3 participants at or near below the limit of quantitation (BLQ). In patient

**Table 1.** Characteristics of patients at baseline.

Characteristic	N-803	N-803	N-803	All Participants(N = 9)
	100 µg(N = 3)	200 µg(N = 3)	400 µg(N = 3)	
Median Age (range) – yr	70 (43–70)	75 (64–78)	65 (61–65)	65 (43–78)
Female sex – no. (%)	1 (33%)	0	0	1 (11%)
Ethnicity – no. (%)				
Not Hispanic or Latino	3 (100%)	3 (100%)	3 (100%)	9 (100%)
Race – no. (%)				
Asian	3 (100%)	1 (33%)	2 (67%)	6 (67%)
White	0	1 (33%)	1 (33%)	2 (22%)
Other	0	1 (33%)	0	1 (11%)
Mean time from diagnosis to study entry (range) – mo	1.95 (1.1–2.7)	2.06 (1.0–3.1)	2.28 (1.8–3.3)	2.1(1.0–3.3)
Urothelial Carcinoma (%)	3 (100%)	3 (100%)	3 (100%)	9 (100%)
High Grade – no. (%)	3 (100%)	3 (100%)	3 (100%)	9 (100%)
High Risk – no. (%)	3 (100%)	3 (100%)	3 (100%)	9 (100%)
T Stage – no. (%)				
Tis	0	1 (33%)	1 (33%)	2 (22%)
Ta	1 (33%)	0	1 (33%)	2 (22%)
T1	2 (67%)	2 (67%)	1 (33%)	5 (56%)
Numbers of Tumors – no. (%)				
1	2 (67%)	2 (67%)	1 (33%)	5 (56%)
2	0	1 (33%)	2 (67%)	3 (33%)
3	1 (33%)	0	0	1 (11%)
Mean dimension of largest tumor – cm	2.8	1.7	2.3	2.3
Immediate postoperative intravesical chemotherapy	1 (33%)	1 (33%)	2 (67%)	4 (44%)
Mean time from last cystoscopy to study entry (range) – mo	0.92 (0.8–1.1)	0.35 (0.3–0.5)	0.48 (0.3–0.7)	0.58 (0.3–1.1)
Mean time from last TURBT to study entry (range) – mo	1.34 (0.8–2.1)	3.06 (1.0–3.1)	1.41 (0.6–1.8)	1.60 (0.6–3.1)
Mean follow-up – mo	61.7	71.3	63.3	65.2

**Table 2.** Summary of treatment related AEs occurring in ≥5% of patients.

	Total		Cohort 1 Grade1-2 ALT-803 100 µg		Cohort 2 Grade1-2 ALT-803 200 µg		Cohort 3 Grade1-2 ALT-803 400 µg	
	(N = 9)	% of total	(N = 3)	%	(N = 3)	%	(N = 3)	%
<b>Any AEs</b>	<b>9</b>	<b>100</b>	<b>3</b>	<b>100</b>	<b>3</b>	<b>100</b>	<b>3</b>	<b>100</b>
<b>Fatigue</b>	<b>3</b>	<b>33</b>	<b>1</b>	<b>33</b>	<b>1</b>	<b>33</b>	<b>1</b>	<b>33</b>
<b>Urinary tract infection</b>	<b>2</b>	<b>22</b>	<b>1</b>	<b>33</b>	<b>0</b>	<b>0</b>	<b>1</b>	<b>33</b>
<b>Headache</b>	<b>2</b>	<b>22</b>	<b>1</b>	<b>33</b>	<b>1</b>	<b>33</b>	<b>0</b>	<b>0</b>
<b>Hematuria</b>	<b>3</b>	<b>33</b>	<b>0</b>	<b>0</b>	<b>2</b>	<b>67</b>	<b>1</b>	<b>33</b>
<b>Urinary urgency</b>	<b>2</b>	<b>22</b>	<b>2</b>	<b>67</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>
<b>Urinary frequency</b>	<b>3</b>	<b>33</b>	<b>2</b>	<b>67</b>	<b>0</b>	<b>0</b>	<b>1</b>	<b>33</b>
<b>Urinary tract pain</b>	<b>2</b>	<b>22</b>	<b>2</b>	<b>67</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>
<b>Dyspnea</b>	<b>2</b>	<b>22</b>	<b>0</b>	<b>0</b>	<b>1</b>	<b>22</b>	<b>1</b>	<b>22</b>
<b>Hypertension</b>	<b>6</b>	<b>67</b>	<b>2</b>	<b>67</b>	<b>2</b>	<b>67</b>	<b>2</b>	<b>67</b>

**Note – There were no grade 3–5 toxicities noted.**

#1, the 24-h post-instillation sample recorded 4.42 pg/mL of N-803. In patient #2 the pre-instillation sample recorded 10.59 pg/mL of N-803, which was BLQ (BLQ; <23.4 pg/mL). In patient #8, the 24-h post-instillation sample recorded 25.13 pg/mL of N-803. N-803 was not detected in any other participants' serum samples; thus, no notable systemic levels were observed. Additionally, no constitutional symptoms were observed in any subject.

### Immunogenicity

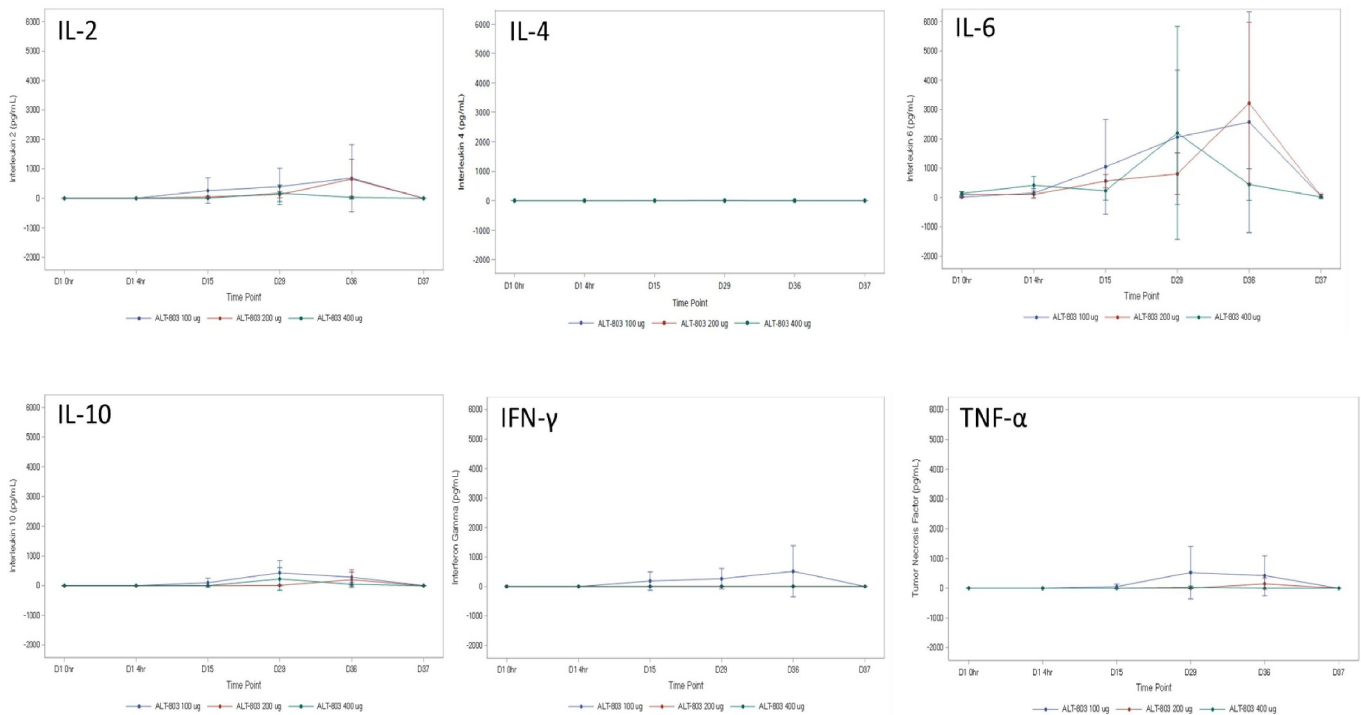
In all 9 participants who received doses of N-803 plus BCG, minimal or negative serum levels of anti-N-803 antibodies were recorded. The sample for week 12 for patient #9 was not tested. However, the prior sample collected at week 6 day 36 (pre-dose) was negative. No anti-N-803 antibodies

were detected in any participants' serum samples at any time.

### Measures of interest

All 9 participants had urine and peripheral blood samples collected and analyzed for cytokines at all time points during the course of the study. Intravesical administration of N-803 in combination with BCG noted an increase in urinary IL-6 levels. Small changes in urinary IL-2, IL-10, TNF- $\alpha$ , and IFN- $\gamma$  were observed (Figure 2). No changes in IL-4 were observed nor was there a correlation between dose levels of N-803 and any urinary cytokine level.

While a slight elevation in serum IL-6 levels were observed following intravesical administration of N-803 in combination with BCG, there was minimal or no change observed in the



**Figure 2. Mean ( $\pm$  SD) Urine levels of cytokines following N-803+ BCG administration.** measurement of cytokine bead array at various time points following the first N-803+ BCG administration. IL-6 peaked 29–36 d after administration.

serum levels of IL-2, IL-4, IL-10, TNF- $\alpha$ , and IFN- $\gamma$  (*Supplemental Table*).

No subject experienced disease recurrence while on study; therefore, only tumors that had been biopsied or resected prior to study entry underwent molecular analyses. All initial biopsy or bladder tumor resection samples were centrally reviewed and confirmed and tested positive by immunohistochemical staining for CD3+, CD4+, CD8+ cells. Scant CD56+ cells were seen in some tissue samples of 4 participants. In follow-up, only 2 participants were noted to have abnormalities on cystoscopy (persistent erythema). Histologic evaluation at 24 weeks of one of these participants confirmed no tumor and significant infiltration of CD3+, CD4+, CD8+ cells, while CD56+ infiltration was minimal, yet higher than baseline (*Supplemental Figure*).

### Treatment response

At the 3-month (week 12) response assessment, a complete response (CR) or lack of recurrence/progression was observed in 7 of 9 (78%) patients. One subject had a 2–3 cm erythematous patch on the left posterior bladder wall noted on cystoscopy at week 12 but did not undergo a biopsy until week 24, which confirmed the subject was disease free. A second subject was noted to harbor a 1 cm erythematous patch on the floor of the bladder and underwent a biopsy at week 12 that showed some dysplasia but was not classified as definitive CIS. The subject continued treatment and had normal cystoscopies for the rest of the study; however, due to the absence of urine cytology tests, was determined inconclusive at week 24 and month 9. At the 6-month (week 24) response assessment, 8 of 9 (89%) participants experienced a CR or lack of recurrence/progression. Six years after treatment, 8 participants (88.9%)

**Table 3. Patient characteristics and outcome.**

Subject Number	Stage	Response Assessment		Follow Up					
		Month 3 (Week 12)	Month 6 (Week 24)	Month 9	Month 12	Month 15	Month 18	Month 21	Month 24
1	T1	NR	NR	NR	NR	NR	NR	NR	NR
2	Ta	NR	NR	NR	NR	NR	ND	NR	NR
3	T1	NR	NR	NR	NR	NR	NR	NR	NR
4	T1	IC	NR	NR	NR	NR	ND	NR	NR
5	CIS	No CR	IC	IC	CR	CR	CR	CR	CR
6	T1	NR	NR	NR	NR	NR	NR	NR	NR
7	T1	NR	NR	NR	NR	NR	NR	NR	NR
8*	CIS	CR	CR	CR	CR	CR	CR	CR	IC
9	Ta	NR	NR	NR	NR	NR	NR	NR	NR

CR = complete response; NR = no recurrence; no CR = no complete response; IC = inconclusive; ND = not done

\*, only subject to develop a recurrence. Noted at 38 months (CIS), which was treated off study with re-induction with N-803 and BCG, followed by maintenance BCG. After another 28 months of follow-up, subject is disease-free with an intact bladder.

were disease free with an intact bladder; mean follow-up 65.2 months (5.4 y), while only patient #8 developed a recurrence at 38 months (CIS), which was treated off study with re-induction with N-803 and BCG, followed by maintenance BCG. After another 28 months of follow-up, patient #8 remains disease-free with an intact bladder. Thus, no patient had disease progression (Table 3).

## Discussion

Notable findings regarding a specific CD122/132 receptor agonist, N-803, in combination with BCG included acceptable toxic effects, which allowed for timely dose escalation, low immunogenicity and major responses, and prolonged disease-free survival in high-risk NMIBC patients. In particular, no SAEs or unique AEs were reported, and all AEs were manageable by standard guidelines. Interestingly, hypertension noted within the treatment facility was the most common adverse event (67%). This could be due to several reasons; a) the treatment entails urethral catheterization which evokes anxiety in many patients and the procedure required the subjects to abstain from voiding for 2 h, which can be associated with discomfort and/or anxiety. Moreover, the safety profile of BCG plus N-803 was consistent with previous reports of BCG alone.<sup>15</sup> Because the MTD was not reached, the dose level of 400 µg N-803 per instillation deemed was safe and thus selected as the recommended dose for the phase 2 expansion study in patients with high-risk BCG-naïve NMIBC. The phase 2 study is currently ongoing (NCT02138734).

Encouragingly, the combination of N-803 plus BCG shows an improvement in durability of response at 12 and 24 months in BCG-naïve NMIBC, in comparison to the historical CR of ≤50% observed in BCG-naïve NMIBC treated with BCG alone.<sup>8</sup>

In preclinical studies, the IL-15-based agonist N-803 potently enhances the activity of the innate and adaptive immune systems against various solid tumor and hematologic malignancies<sup>16</sup> and is superior to BCG monotherapy for the treatment of carcinogen-induced NMIBC in murine models.<sup>13,17</sup>

Combination immunotherapy regimens may increase the response rate to intravesical BCG therapy, thus increasing the number of patients with NMIBC who could derive long-term clinical benefit from BCG therapy. NMIBC is an ideal disease to develop combinations of nonsystemic local immune therapies with complementary NK and CD8 + T-cell immune mechanisms to clear local early disease with durable responses. The preliminary clinical data generated in this study further supports the unique mechanism of action offered by N-803 with BCG through the production and stimulation of and CD8 + T cells<sup>13</sup> known to be responsible for inducing immune clearance of bladder tumor cells. This data is further substantiated by the treatment and response of a 91-year-old patient with BCG-unresponsive high-grade NMIBC whose disease failed to respond to intravesical valrubicin and gemcitabine and a 65-year-old patient whose disease failed to respond to previous BCG therapy. Both tumors were noted to express high levels of the immunosuppressive factors cytotoxic T-lymphocyte associated protein (CTLA)-4 and CD39 and both were treated with N-803 plus BCG therapy.

Subsequently, both patients were noted to be disease free at 12 and 24 months.<sup>18</sup> Taken together, the data suggest that NMIBC tumors surrounded by an immunosuppressive microenvironment as compared to tumors without an immunosuppressive microenvironment may respond better to N-803 immunotherapy when prior BCG therapy has failed. Based on these data, a single-arm phase 2 study assessing N-803 in combination with BCG in patients who have failed prior BCG therapy is currently ongoing (NCT NCT03022825).

The results from this trial are in line with those from separate preclinical studies noting additive tumor suppressive effect when combining N-803 with cetuximab in squamous cell carcinoma of the head and neck,<sup>19</sup> sunitinib in melanoma<sup>20</sup> and rituximab in Burkitt lymphoma.<sup>21</sup> Furthermore, Wrangle *et al.* reported a phase 1 clinical trial of N-803 in combination with nivolumab in patients previously treated with platinum and PD-1 inhibitors to be safe and tolerable in an outpatient setting with a 29% overall objective response rate linked to the expansion of NK and CD8 + cells.<sup>22</sup> The totality of the emerging data suggests that local administration of an immune therapy (BCG) that induces immune clearance by an NK and CD8 + T-cell dependent mechanism can be combined safely with an IL-15 cytokine super-agonist known to enhance NK and CD8 + T-cell proliferation and function. Six years after treatment, all 9 participants (100%) were disease free with an intact bladder. No patients had disease progression, and only one recurrence was noted; although historical data would suggest a recurrence rate of 30–80% and 10–20% of recurrent cases progressing to muscle invasive bladder cancer.<sup>7,8,23</sup> This combination demonstrates potential efficacy to aid in tumor clearance, reducing the likelihood that patients with NMIBC will experience disease progression to a more serious condition, without systemic toxicity, thus it is another immunotherapy joining the ranks of the checkpoint inhibitors and IFN-alpha-2b. It also shows the potential for utilizing N-803 in other settings of cancer and infectious diseases where enhanced NK cell and CD8 + T-cell activation and proliferation act to further immune-mediated clearance of these diseases.

Findings from this study should be interpreted in the context of its early-phase design, particularly the small number of patients enrolled, which limits data robustness and reduces the potential for subgroup analyses. In addition, the single-arm, non-randomized design prevents any direct comparison with alternative treatment options in this disease setting.

In this phase 1b trial of subjects with BCG-naïve NMIBC, combination therapy of N-803 with BCG has been shown to exhibit antitumor activity with a favorable safety profile. Treatment with N-803 plus BCG is well tolerated with very low toxicity and low immunogenicity. Thus, further studies investigating this novel therapy for patients with high-risk NMIBC are warranted.

## Disclosure statement

In accordance with Taylor & Francis policy and my ethical obligation as a researcher, I am reporting that the study was funded by Altor Bioscience, a company that may be affected by the research reported in the enclosed paper. I have disclosed those interests fully to Taylor & Francis, and I have in place an approved plan for managing any potential conflicts.

## Disclosure statement

Irinia Ianculescu, Sandeep Reddy and Patrick Soon-Shiong are employees of ImmunityBio, Inc. and NantHealth Inc. Charles J. Rosser, Sergei Tikhonenkov, Jeffrey W. Nix, Owen TM Chan have no competing interests.

## Funding

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