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ORIGINAL ARTICLE

IL-15 Superagonist NAI in BCG-Unresponsive Non–Muscle-Invasive Bladder Cancer

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Abstract

BACKGROUND Patients with Bacillus Calmette–Guérin (BCG)–unresponsive non–muscle-invasive bladder cancer (NMIBC) have limited treatment options. The immune cell–activating interleukin-15 (IL-15) superagonist Nogapendekin alfa inbakicept (NAI), also known as N-803, may act synergistically with BCG to elicit durable complete responses (CRs) in this patient population.

METHODS In this open-label, multicenter study, patients with BCG-unresponsive bladder carcinoma in situ (CIS) with or without Ta/T1 papillary disease were treated with intravesical NAI plus BCG (cohort A) or NAI alone (cohort C). Patients with BCG-unresponsive high-grade Ta/T1 papillary NMIBC also received NAI plus BCG (cohort B). The primary end point was the incidence of CR at the 3- or 6-month assessment visit for cohorts A and C, and the disease-free survival (DFS) rate at 12 months for cohort B. Durability, cystectomy avoidance, progression-free survival, disease-specific survival (DSS), and overall survival were secondary end points for cohort A.

RESULTS In cohort A, CR was achieved in 58 (71%) of 82 patients (95% confidence interval [CI]=59.6 to 80.3; median follow-up, 23.9 months), with a median duration of 26.6 months (95% CI=9.9 months to [upper bound not reached]). At 24 months in patients with CR, the Kaplan–Meier estimated probability of avoiding cystectomy and of DSS was 89.2% and 100%, respectively. In cohort B (n=72), the Kaplan–Meier estimated DFS rate was 55.4% (95% CI=42.0% to 66.8%) at 12 months, with median DFS of 19.3 months (95% CI=7.4 months to [upper bound not reached]). Most treatment-emergent adverse events for patients receiving BCG plus NAI were grade 1 to 2 (86%); three grade 3 immune-related treatment-emergent adverse events occurred.

Drs. Chamie and Chang contributed equally to this article and are coprincipal investigators.

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CONCLUSIONS In patients with BCG-unresponsive bladder carcinoma in situ and papillary NMIBC treated with BCG and the novel agent NAI, CRs were achieved with a persistence of effect, cystectomy avoidance, and 100% bladder cancer–specific survival at 24 months. The study is ongoing, with an estimated target enrollment of 200 participants (Funded by ImmunityBio.)

Introduction

Globally, bladder cancer is the 10th most commonly diagnosed cancer and has the highest lifetime treatment costs per patient as a result of the prolonged course of the disease and the need for repeated surgical and treatment interventions.[1,2] Roughly 80% of new bladder cancer diagnoses are non–muscle-invasive bladder cancer (NMIBC).[3] Patients with intermediate or high-risk NMIBC typically receive a treatment of transurethral resection of the bladder tumor (TURBT) followed by Bacillus Calmette–Guérin (BCG) intravesical instillation. However, cancer will recur in 30 to 40% of patients with NMIBC despite adequate treatment with BCG. Moreover, even among those in whom a complete response (CR) is achieved with BCG, up to 50% will experience relapse.[4,5] Patients with BCG-unresponsive NMIBC are extremely unlikely to benefit from additional BCG therapy and represent a patient population in need of novel treatment options.[6]

Current treatment options are limited. Pembrolizumab has been approved recently for the treatment of BCG-unresponsive NMIBC, and although a CR was achieved in 41% of patients treated with pembrolizumab in a phase II study, less than one half of responders continued to receive therapy and remained disease free 1 year after initiation of treatment.[7] Moreover, treatment with pembrolizumab was associated with immune-related toxicities.

Radical cystectomy can be a curative option for patients with NMIBC,[8] but it requires major surgery that is associated with a high morbidity and mortality rate, particularly among the elderly who comprise the majority of the population of patients with NMIBC.[9] Prognosis for patients with high-risk NMIBC is poor, with approximately 20% of patients experiencing progression to muscle-invasive disease and 14% of patients dying from bladder cancer.[10]

Increasing evidence suggests impaired T-cell and cytotoxic cellular responses play a role in BCG therapy failure.[11,12] Nogapendekin alfa-inbakicept (NAI), previously referred to as N-803, an interleukin 15 (IL-15) superagonist, is a fusion protein of a human IL-15 variant bound to a dimeric human IL-15Rα sushi domain/human IgG1 Fc.[13] This IL-15–based immunostimulatory protein complex acts as an activation and proliferation factor for natural killer (NK) cells as well as effector and memory T cells. It has been postulated recently that BCG establishes so-called trained immunity as the molecular basis for its immunotherapeutic effect in bladder cancer and that this trained immunity may be enhanced with a second unrelated stimulus.[14] We hypothesized that NAI could act as this secondary unrelated stimulus, induce proliferation of NK and T cells,[15] and synergistically enhance BCG efficacy. The potential synergy of BCG combined with NAI in the treatment of patients with BCG-unresponsive NMIBC was preliminarily assessed in a completed phase I trial[16] and further assessed in the clinical study reported herein, known as QUILT-3.032.

Methods

QUILT-3.032 (NCT03022825; see the protocol provided with the full text of this article at evidence.nejm.org) is an ongoing registrational, pivotal, open-label, single-arm, three-cohort, multicenter trial (32 clinical trial sites) of intravesical NAI (Anktiva; ImmunityBio) plus BCG or NAI alone in patients with BCG-unresponsive high-grade NMIBC. Given the lack of effective treatment alternatives for this patient population and per Food and Drug Administration guidance and agreement, QUILT-3.032 was designed as a single-arm study.[6]

PATIENTS

Patients were enrolled in one of three study cohorts. Cohorts A and C enrolled patients with histologically confirmed BCG-unresponsive carcinoma in situ (CIS) with or without Ta/T1 papillary disease. Cohort B enrolled patients with histologically confirmed BCG-unresponsive high-grade Ta/T1 papillary NMIBC. Patients had to be absent of resectable disease after TURBT procedures, and those with high-grade Ta and/or T1 disease had a complete resection before study treatment. For inclusion in this study, male and female patients had to be 18 years of age or older. Key exclusion criteria included life expectancy of less than 2 years, inadequate organ function, clinical signs of severe cardiac dysfunction, and history or evidence of muscle-invasive, locally advanced, metastatic and/or extravesical bladder cancer, or any other

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cancer, other than nonmelanoma skin cancer, within the past 5 years. The definitions of BCG-unresponsive NMIBC, inadequate organ function, and signs of severe cardiac dysfunction are presented in the Supplementary Appendix (p. 2) available with the full text of this article at evidence.nejm.org.

TREATMENTS AND ASSESSMENTS

Patients in cohorts A and B were treated with intravesical NAI (400 μg/instillation) plus intravesical BCG (50 mg/instillation). Patients in cohort C received intravesical NAI alone (400 μg/instillation). All patients received study treatment through a urinary catheter in the bladder weekly for 6 consecutive weeks during the induction treatment period. Response assessments were to be completed every 3 months through month 24 and every 6 months from month 24 to month 60 for all cohorts. Cystoscopy was performed at each response assessment and urine collected — either by voided specimen or during cystoscopy — for urine cytology. Continued treatment on study was dependent on the response recorded at assessments as noted below. Biopsy was required at week 12 (approximately 3 months). Patients in all cohorts in whom a response was not achieved and who had no T1 or greater disease were offered the option of reinduction. Biopsy was required at month 6 for all patients who were reinducted at week 12. Details on response assessments and adjustments to therapy, including reinduction or maintenance therapy, on the basis of these assessments are provided in the Supplementary Appendix (p. 2-3).

Because it was anticipated that efficacy would be dependent upon the synergy of the NAI and BCG effects, treatment with NAI monotherapy in cohort C followed a Simon's two-stage design (Supplementary Appendix [p. 3]), which minimized the number of patients enrolled if NAI alone had low efficacy.

Cohorts A, B, and C are independent study cohorts and were evaluated separately for efficacy. Herein, we report efficacy and safety data for all three cohorts. The efficacy population in each cohort included patients with BCG-unresponsive NMIBC who had reached the 3-month response assessment or discontinued treatment before that assessment at the time of the January 15, 2022, data cutoff. The safety populations consisted of all patients in each cohort who received at least one instillation of the study drug.

END POINTS

The primary end point for cohorts A and C was defined as the incidence of CR at the 3- or 6-month response assessment visit (CR rate at any time) on the basis of investigator assessment of urine cytology, cystoscopy, and local pathology results. CR was defined as negative cystoscopy and negative, including atypical, urine cytology; positive cystoscopy with biopsy-proven benign or low-grade Ta NMIBC and negative cytology; or negative cystoscopy with malignant urine cytology if cancer was found in the upper tract or prostatic urethra and random bladder biopsies were negative.

As a secondary end point, responses were assessed by blinded central pathology review.

To meet the primary end point in cohort A, the lower limit of the 95% confidence interval (CI) of the CR rate at any time had to exceed 20%. Our design was based on achieving a 30% CR rate at any time in this population. This led to a sample size of at least 76 patients to achieve a two-sided 95% CI, with a lower limit greater than 20% when the CR rate of this population is 30%. Secondary efficacy end points include durability of response, cystectomy avoidance rate, progression-free survival (PFS), disease-specific survival (DSS), and overall survival (OS). All objectives were exploratory for cohort C and included efficacy end points of the incidence of CR and duration of CR. Power analysis for cohort C is presented in the Supplementary Appendix (p. 3).

The primary end point for cohort B was the disease-free survival (DFS) rate at 12 months since the first instillation of BCG plus NAI, with disease free defined as the absence of high-grade Ta (excluding low-grade Ta), any grade T1, persistent CIS of 6 months or more, new CIS, disease progression, cystectomy, change in therapy indicative of more advanced disease, and death (any cause). Our design was based on achieving a 30% disease-free rate at 12 months in this population. A sample size of more than 76 patients produces a two-sided 95% CI with a lower limit of 20% when the disease-free rate at 12 months was 30% for this population.

Safety was assessed by the incidence and severity of treatment-emergent adverse events (TEAEs), adverse events of special interest, clinical laboratory assessments, vital signs, treatment exposure, concomitant medications, immunogenicity, and physical examinations for all patients who received at least one dose of the study treatment. All TEAEs were reported regardless of assumed causality and were graded using Common Terminology Criteria for Adverse Events v4.03 and coded using the Medical Dictionary for Regulatory Activities.

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STATISTICAL ANALYSIS METHODS

For cohorts A and C, the primary end point — CR at any time — was analyzed using a two-sided exact 95% CI calculated using the Clopper-Pearson method. All time-to-event end points, including duration of CR, PFS, DSS, OS, and (for cohort B) DFS rate, were assessed using Kaplan–Meier analysis methods. Descriptive statistics were used to summarize the demographic, baseline, and safety data from this study. The statistical analysis plan is provided in the Supplementary Appendix. The handling of missing data is described in the Supplementary Appendix (p. 3-4).

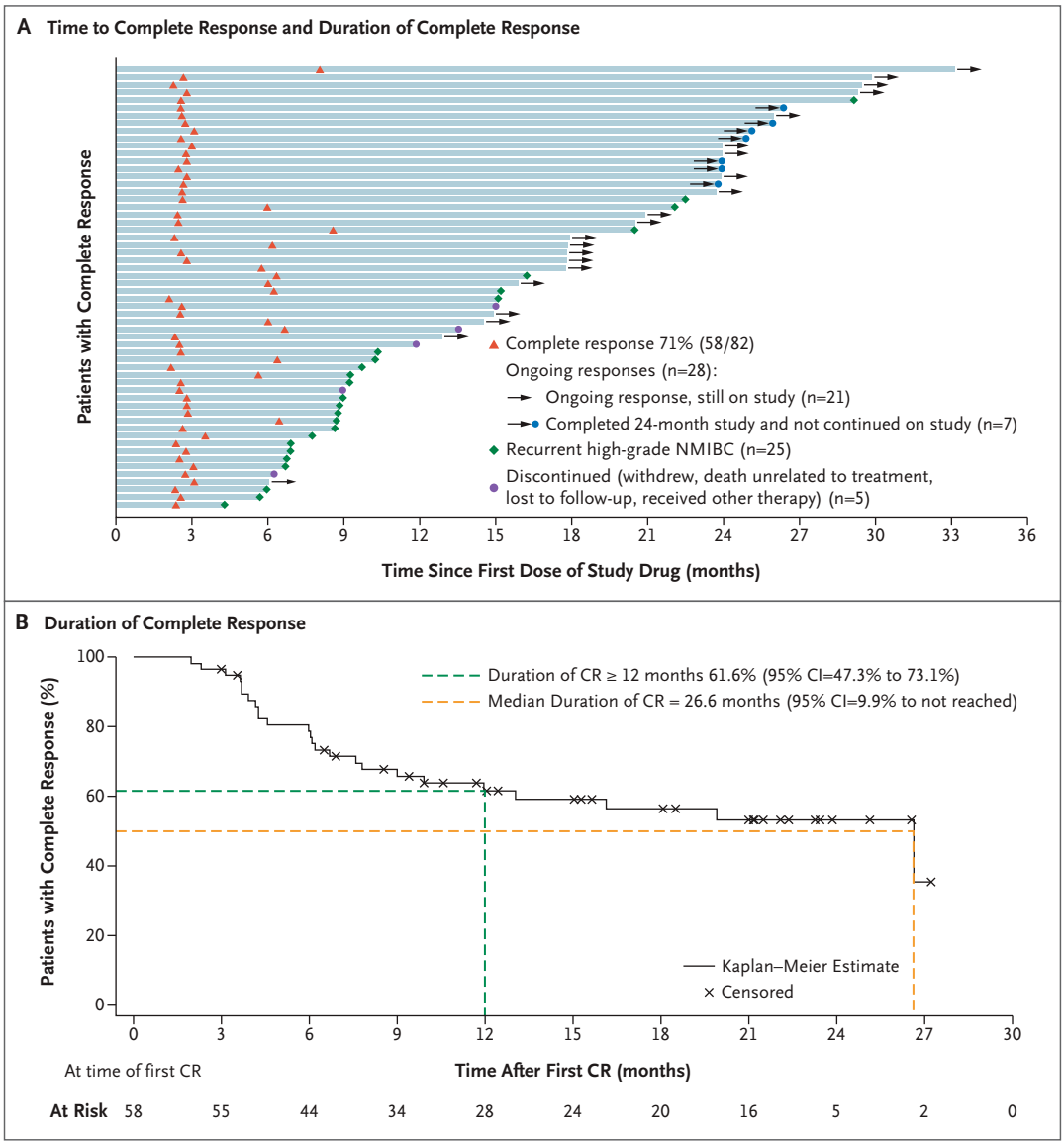

Figure 1. Duration of Complete Response, Disease Progression, and Survival in Cohort A Patients with Carcinoma In Situ.

(Panel A) Time to complete response (CR) and duration of CR for individual patients are shown. (Panel B) Duration of response showing probability of duration ≥12 months and median duration of CR (26.6 months) are shown. (Panel C) Progression-free survival (PFS), overall survival (OS), and disease-specific survival (DSS) for the cohort A efficacy population with rates at 24 months are shown. Panels B and C are graphed using Kaplan–Meier methods. CI denotes confidence interval; NMIBC, non–muscle-invasive bladder cancer.

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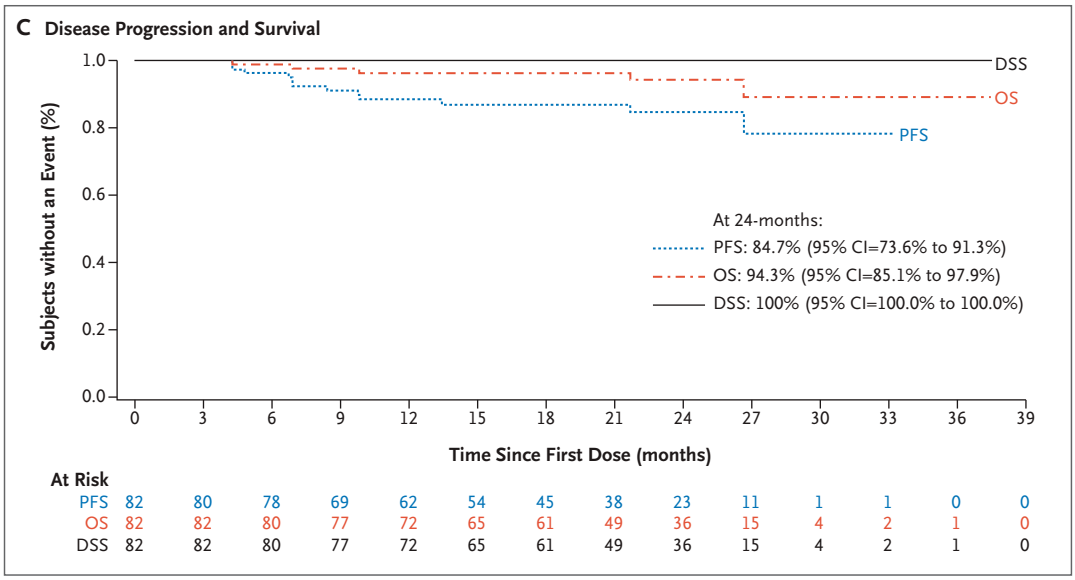

Figure 1. Continued.

TRIAL OVERSIGHT

This trial was designed by the sponsor ImmunityBio. Ethics bodies at each participating institution approved the protocol and any amendments. The study was conducted in accordance with the International Conference on Harmonization for Good Clinical Practice guidelines[17] and with the principles of the Declaration of Helsinki. Written consent was given by all study participants before enrollment. Data were gathered by study investigators and analyzed by Biostatistics at ImmunityBio. DCL Pathology (Greenwood, IN) performed the central pathology review. The sponsor, ImmunityBio, vouches for the data and, along with all authors, made the decision to publish the paper. The manuscript was written by authors P. Spilman, P. Soon-Shiong, S. Reddy, S. A. Taha, P. Bhar, and M. Huang; P. Spilman wrote the first draft. All authors had access to the data used to prepare the manuscript and participated in the writing or critical review and editing of the manuscript. All authors approved the submitted manuscript and assure the accuracy and completeness of the data reported and the fidelity of the trial to the protocol.

Results

PATIENT DEMOGRAPHICS AND TREATMENT

Between July 2017 and January 2022, a total of 171 patients were enrolled at 22 of the 32 clinical trial sites, all based in the United States. A total of 84 patients were enrolled in cohort A, 77 in cohort B, and 10 in cohort C. Patient enrollment, treatment, and disposition are shown in Figure S1 in the Supplementary Appendix (p. 5).

For cohorts A, B, and C, respectively, the median age of patients in the efficacy populations was 73 (range, 50 to 91), 72 (range, 46 to 93), and 74.5 (range, 67 to 82) years (Table S1, p. 7). Most patients were male (87%, 74%, and 60%) and White (90%, 88%, and 90%) in cohorts A, B, and C, respectively; for cohort A, this was a higher proportion of White males than is reported in data available through the Surveillance, Epidemiology, and End Results Database for NMIBC and bladder cancer (Table S2, p. 8). The majority of patients (81%, 77%, and 60% in cohorts A, B, and C, respectively) had a baseline Eastern Cooperative Oncology Group performance status score of 0 (ranging from 0, indicating the patient was fully active and able to carry out all predisease performance without restriction, to 5, indicating death). Median time from last TURBT to study enrollment for cohorts A, B, and C was 1.43 months, 1.31 months, and 1.40 months, respectively.

EFFICACY IN COHORT A — CR AND DURATION OF RESPONSE

The efficacy population in cohort A consisted of 82 evaluable patients (two patients on study had not reached the 3-month response assessment at the time of data cutoff),

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with a median follow-up duration of 23.9 months (range, 3.2 to 37.5 months).

Overall, a CR at any time was achieved in 71% of patients (58 of 82; 95% CI=59.6% to 80.3%). This included 45 patients who experienced a response to initial treatment and 13 patients who received reinduction therapy. At the 3-, 6-, and 12-month response assessments, CR rates were 55% (45 of 82 patients; 95% CI=43.5% to 65.9%), 56% (46 of 82 patients; 95% CI=44.7% to 67.0%), and 45% (37 of 82 patients; 95% CI=34.1% to 56.5%), respectively. Median duration of CR in responders was 26.6 months (95% CI=9.9 months to [upper bound not reached]). Of the 58 patients with CR, there were 28 patients with ongoing CRs at the time of data cutoff or withdrawal from the study (Fig. 1A). Two patients had initial CRs that were first recorded at approximately 9 months as a result of the coronavirus disease 2019 pandemic or other illness-related delays of the month 6 visit.

Responses to treatment in 77 patients had been evaluated by blinded central pathology review at the time of data cutoff; central and local pathology were concordant for 53 (98%) of 54 patients who had a CR. The absence of a CR was concordant for 19 (83%) of 23 patients. Overall, the incidence of CR at any time determined by central pathology was 74% (57 of 77 patients; 95% CI=62.8% to 83.4%), comparable to the 71% as assessed by local pathology.

On the basis of Kaplan–Meier methods, the probability of duration of CR for 12 months or longer was 61.6% (95% CI=47.3% to 73.1%) and the probability of duration of CR for 24 months or longer was 53.2% (95% CI=38% to 66.2%; Fig. 1B). Overall, 45% of all patients in cohort A

Table 1. Summary of Efficacy in Cohort A.*

Response	Value	
Complete response — no. of patients	58/82	
CR rate (95% CI)	71% (59.6, 80.3)	
Median duration of follow-up — mo	23.9	
Range of follow-up of all patients — mo	4.3–37.5	
Prior BCG dose level — CR rate (95% CI)		
Full dose prior BCG (n=71)	69 (56.9–79.5)	
Reduced dose prior BCG (n=11)	82 (48.2–97.7)	
Duration of Response		
Median — mo (95% CI)	26.6 (9.9 to upper bound not reached)	
Probability of DoR ≥12 mo — % (95% CI)†	61.6 (47.3–73.1)	
Patients with DoR ≥12 mo — % (n/N)	37 (30/82)	
Patients with DoR ≥18 mo — % (n/N)	24 (20/82)	
Progression-free survival rate — % (95% CI)†‡	**Responders**	**All**
12 mo	91.1 (79.8–96.2)	88.4 (78.9–93.8)
18 mo	91.1 (79.8–96.2)	86.9 (77.0–92.8)
24 mo	88.1 (74.9–94.6)	84.7 (73.6–91.3)
Disease-specific survival — % (95% CI)†§		
12 mo	100 (100.0–100.0)	100 (100.0–100.0)
24 mo	100 (100.0–100.0)	100 (100.0–100.0)
Overall survival — % (95% CI)†		
12 mo	94.8 (84.6–98.3)	96.2 (88.8–98.8)
18 mo	94.8 (84.6–98.3)	96.2 (88.8–98.8)
24 mo	92.1 (79.7–97.0)	94.3 (85.1–97.9)
Cystectomy rate in responders — % (n/N)	9 (5/58)	16 (13/82)

* Response to treatment, survival, and cystectomy rate in cohort A (n=82) are shown. BCG denotes Bacillus Calmette–Guérin; CI, confidence interval; and CR, complete response.

† Kaplan–Meier analysis methods were used.

‡ Progression-free survival is the time from first study drug administration to disease progression or death from any cause.

§ Disease-specific survival is the time from initial study drug administration to death resulting from bladder cancer.

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(37 of 82 patients) had a CR at the 12-month response assessment, and 33% (27 of 82 patients) had a CR at the 18-month response assessment.

At 24 months, the probability of PFS was 84.7%; OS, 94.3%; and DSS, 100% by the Kaplan–Meier analysis, as shown in Figure 1C. Disease progression and survival for all patients are summarized in Table 1.

SUBGROUP ANALYSIS

Potential response heterogeneity in cohort A patients was assessed in predefined subgroup analyses (Fig. 2). The lower bound of the 95% CI of the CR rate was greater than 20% for all subgroups, with the exception of female patients, in which it was 16.7%. CR rates for patients with baseline disease types of CIS alone, CIS/Ta disease, and CIS/T1 disease (noting that only nine patients had CIS/T1) were 68% (95% CI=54.8% to 80.1%), 81% (95% CI=54.4% to 96.0%), and 67% (95% CI=29.9% to 92.5%), respectively; with 12 doses or more of prior BCG and fewer than 12 doses, they were 70% (95% CI=57.1% to 80.4%) and 75% (95% CI=47.6% to 92.7%), respectively; and for patients who had received full or reduced doses of BCG before study entry, they were 69% (95% CI=56.9% to 79.5%) and 82% (95% CI=48.2% to 97.7%), respectively.

RESPONSES WITH REINDUCTION

Of the 24 patients who underwent reinduction — an option for patients without a CR and with residual CIS or high-grade Ta at the month 3 assessment visit — a CR was subsequently achieved in a majority (54%; 13 of 24; 95% CI=32.8% to 74.4%). For reinducted patients at 6, 12, and 18 months, response rates were 46% (11 of 24; 95% CI=25.6% to 67.2%), 42% (10 of 24; 95% CI=22.1% to 63.4%), and 21% (5 of 24; 95% CI=7.1% to 42.2%), respectively. The Kaplan–Meier estimated probability of duration of CR 3, 6, 12, 18, and 24 months or longer were 92.3% (95% CI=56.6% to 98.9%), 76.9% (95% CI=44.2% to 91.9%), 43.3% (95% CI=12.7% to 71.1%), 21.6% (95% CI=1.4% to 57.9%), and 21.6% (95% CI=1.4% to 57.9%), respectively.

CYSTECTOMY RATE

In the 71% of patients who experienced response, 7% (4 of 58) subsequently underwent cystectomy for bladder

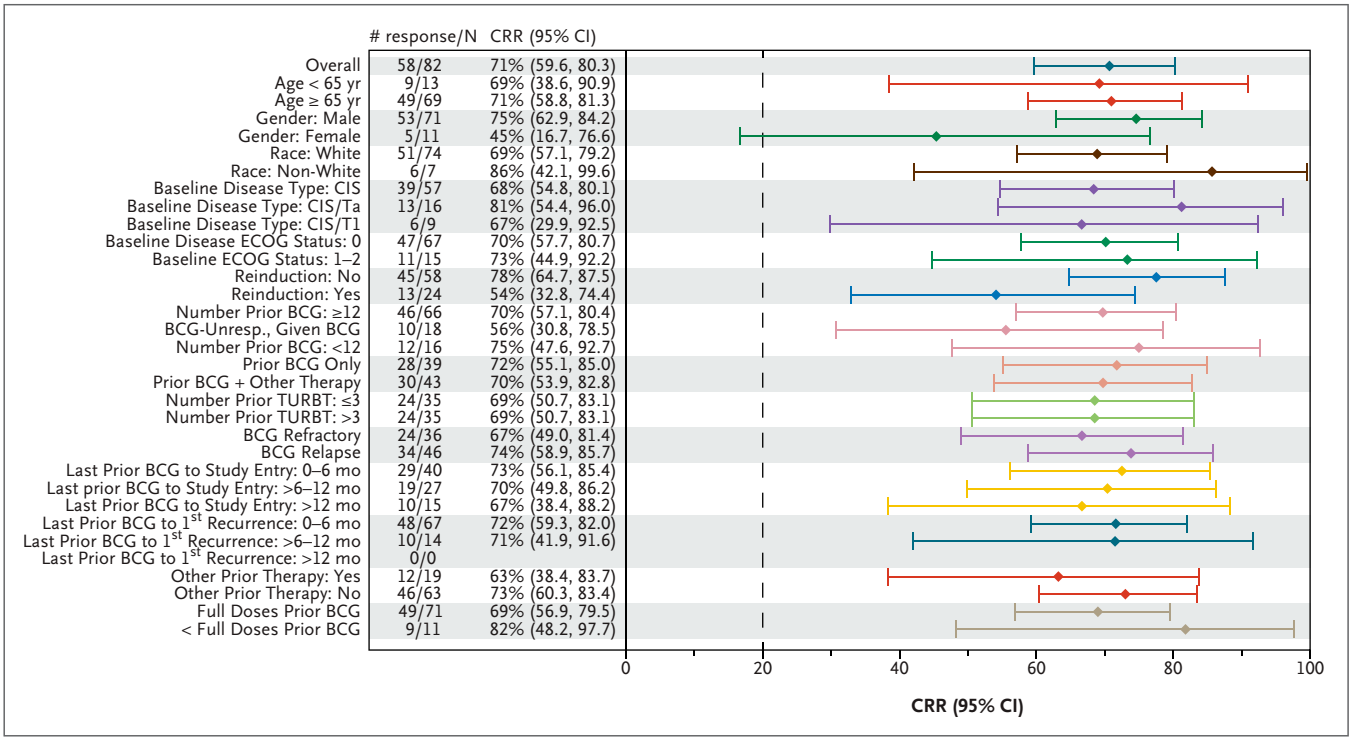

Figure 2. Complete Response Rate (CRR) Across Cohort A Subgroups.

Response rates for subgroups are shown. The vertical dashed line represents the threshold required for the lower limit of the 95% confidence interval (CI) to meet the primary end point. 'BCG-unresp. Given BCG' represents patients previously defined as Bacillus Calmette–Guérin (BCG) unresponsive who were given additional BCG. CIS denotes carcinoma in situ; ECOG, Eastern Cooperative Oncology Group; and TURBT, transurethral resection of the bladder tumor.

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cancer, whereas 33% (8 of 24) who did not experience response had cystectomy. In a fifth patient with a CR, cystectomy was performed for urethral and ureter disease, with no evidence of disease in the bladder at the time of cystectomy. The median time to cystectomy was 11.0 months for responders versus 7.8 months for nonresponders. The Kaplan–Meier estimated probability of remaining cystectomy free for 12 months or longer was 94.3% and 68.5%, and for 24 months or longer was 89.2% and 63.2% in responders and nonresponders, respectively (Fig. S2).

EFFICACY IN COHORT B — DFS

The efficacy population in cohort B consisted of 72 evaluable patients with a median follow-up duration of 20.7 months (range, 2.9 to 37.1 months). Median DFS was 19.3 months (7.4 months to [upper bound not reached]), and DFS rates at 12, 18, and 24 months were 55.4% (95% CI=42.0% to 66.8%), 51.1% (95% CI=37.6% to 63.1%), and 48.3% (95% CI=34.5% to 60.7%), respectively, by Kaplan–Meier analysis. The cystectomy rate was 7% (5 of 72 patients). These data and that for DSS, PFS, and OS are shown in Table 2.

Table 2. Summary of Efficacy in Cohort B.*

Response	Value
Median duration of follow-up — mo	20.7
Range of follow-up of all patients — mo	2.9–37.1
Disease-free survival (n=72)	
Median disease-free survival — mo (95% CI)†	19.3 (7.4 to upper bound not reached)
Disease-free survival rate — % (95% CI)†	
12 mo	55.4 (42.0–66.8)
18 mo	51.1 (37.6–63.1)
24 mo	48.3 (34.5–60.7)
Progression-free survival rate — % (95% CI)†	
12 mo	97.1 (88.8–99.3)
18 mo	94.8 (84.3–98.3)
24 mo	88.8 (74.1–95.4)
Disease-specific survival — % (95% CI)†	
12 mo	100 (100–100)
24 mo	97.7 (84.6–99.7)
Overall survival — % (95% CI)†	
12 mo	98.6 (90.2–99.8)
18 mo	94.3 (82.9–98.1)
24 mo	91.7 (79.0–96.9)
Cystectomy rate — no. (%)	5 (7)

* Disease-free survival, progression-free survival, disease-specific survival, overall survival, and cystectomy rate in cohort B (n=72) are shown. CI denotes confidence interval.

† Kaplan–Meier analysis methods were used.

EFFICACY IN COHORT C — RESPONSES TO NAI MONOTHERAPY

Median follow-up for the 10 patients in cohort C at the time of data cutoff was 7.9 months (range, 4.1 to 11.8 months). A CR at 3 months was achieved in only 2 (20%) of 10 patients who were administered NAI alone. Six patients underwent reinduction. Only one patient (10%) maintained a CR at 6 months. On the basis of protocol-defined stopping rules, the independent data monitoring committee recommended that cohort C be discontinued for futility; enrollment in this cohort was stopped approximately 6 months into study conduct.

SAFETY AND PHARMACOKINETICS

The most frequently reported TEAEs for patients who received BCG plus NAI (cohorts A and B, n=161) were those expected for intravesical instillation of BCG and included dysuria, pollakiuria, and haematuria (Table 3). The overall incidence of grade 1-2, 3, 4, and 5 TEAEs was 86%, 20%, 2%, and 1%, respectively. The most frequent grade 3 TEAEs included hematuria (2%) and urinary tract infection (2%); the incidence of all others was 1%. There was a single incidence (1%) of a grade 5 TEAE (cardiac arrest with an outcome of death) and three grade 3 immune-related TEAEs. TEAEs that required hospitalization occurred in 24 (15%) of 161 patients, of which 8 (5%) were bladder related, with haematuria having the highest incidence (4 of 161 [2%]) and all others having an incidence of 1% (Table S3).

In cohort C patients who received only NAI, 7 (70%) of 10 had at least one TEAE, all of which were grade 1 or 2, with the exception of a stroke of grade 3 severity in one patient that led to hospitalization (Table S4).

Pharmacokinetic analysis of serum NAI levels in a subset of 25 patients after intravesical administration indicated that levels were below the lower limit of quantification of 100 pg/ml in all patients. There was no evidence of systemic NAI in any patient.

Discussion

At the time of the data cutoff for the presented findings, median patient follow-up for cohort A was 23.9 months.

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Table 3. Summary of Safety of Nogapendekin Alfa Inbakicept Plus Bacillus Calmette–Guérin.*				
Summary	**Cohorts A and B Combined (N = 161) — no. (%)**			
Patients with at least 1 TEAE grade 1 or 2	139 (86)			
Patients with at least 1 TEAE grade 3	32 (20)			
Patients with at least 1 TEAE grade 4; or grade 5	3 (2); 1 (1)			
Patients with at least 1 TEAE with outcome of death	1 (1)			
Patients with at least 1 immune-related grade 3 TEAE	3 (2)			
TEAE — no. (%)†	Grade 1–2	Grade 3	Grade 4	Grade 5
Dysuria	49 (30)	1 (1)	0	0
Pollakiuria	41 (25)	1 (1)	0	0
Haematuria	40 (25)	4 (2)	0	0
Urinary tract infection	30 (19)	3 (2)	0	0
Fatigue	30 (19)	0	0	0
Micturition urgency	29 (18)	0	0	0
Chills	19 (12)	0	0	0

* Summary of safety results and most common treatment-emergent adverse events (TEAEs). All patients treated with nogapendekin alfa inbakicept and Bacillus Calmette–Guérin.

† Table shows TEAEs occurring in ≥10% of patients receiving nogapendekin alfa inbakicept and Bacillus Calmette–Guérin.

The CR rate for the BCG-unresponsive NMIBC CIS cohort treated with NAI plus BCG was 71% (95% CI=59.6% to 80.3%) at any time and 45% (37 of 82 patients) and 33% (27 of 82 patients) at 12 and 18 months, respectively, exceeding the 30% suggested as a target for clinical efficacy described in Kamat et al.[18] (a CR rate of at least 30% at 12 months and 25% at 18 months) and established by U.S. Food and Drug Administration experts, the American Urological Association panel, and the International Bladder Cancer Group consensus (a response rate of at least 30% for 18 to 24 months).[19,20]

Subgroup analysis showed that CR rates and durations of response were comparable to those of the primary efficacy population for nearly all subgroups with the exception of people of the female sex. This included subgroups for the number of prior BCG doses or full versus reduced prior BCG dose, suggesting that NAI plus BCG has efficacy independent of prior BCG treatment number or dosage. In analyzing patients by baseline disease, the efficacy of the combination was retained in the subgroup with the highest clinical risk (i.e., CIS/T1) and was comparable to that of other subgroups.

A distinctive feature of the study design was the availability of reinduction in patients with residual CIS or high-grade Ta disease at 3 months. Of the patients enrolled in cohort A, a CR at 3 months was achieved and reinduction therapy not received in 55%. In those patients who did receive reinduction therapy, 54% experienced a response, with the response rate of 42% at 12 months exceeding the suggested targets for efficacy advanced by Kamat et al.[18]

The most common TEAEs reported after NAI plus BCG administration were related to bladder instillation (e.g., dysuria, pollakiuria, and hematuria), and the majority of these TEAEs were grade 1 to 2. This is consistent with pharmacokinetic findings showing no evidence of systemic NAI after intravesical administration.

In conclusion, our data show that NAI plus BCG has benefit in high-risk CIS disease, as evidenced by a CR rate of 71%, a persistence of effect with a median duration of CR of 26.6 months, avoidance of cystectomy in 90% of those with a CR, an 89% probability of patients being cystectomy free at 24 months, and bladder cancer (disease-) specific survival at 24 months of 100% in all patients with CIS. The study is ongoing, with an estimated target enrollment of 200.

Disclosures

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Author disclosures and other supplementary materials are available at evidence.nejm.org.

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