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## **Efficacy of Intravesical Nadofaragene Firadenovec for Patients With Bacillus Calmette-Guérin-Unresponsive Nonmuscle-Invasive Bladder Cancer: 5-Year Follow-Up From a Phase 3 Trial**

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OPEN

## Bladder Cancer

### JU Insight

# Efficacy of Intravesical Nadofaragene Firadenovec for Patients With Bacillus Calmette-Guérin–Unresponsive Nonmuscle-Invasive Bladder Cancer: 5-Year Follow-Up From a Phase 3 Trial

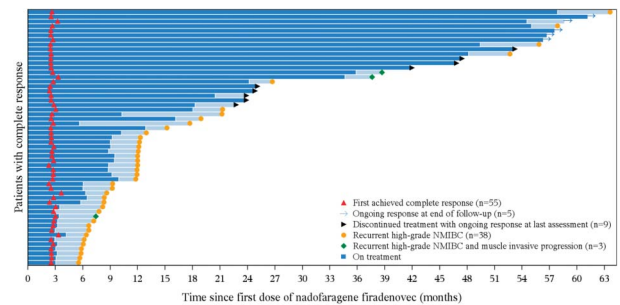
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**Study Need and Importance:** Bacillus Calmette-Guérin (BCG)–unresponsive nonmuscle-invasive bladder cancer (NMIBC) is a challenging clinical condition with limited treatment options. In December 2022, the US Food and Drug Administration approved intravesical nadofaragene firadenovec-vncg (nadofaragene) for the treatment of BCG-unresponsive NMIBC with carcinoma in situ (CIS), with or without papillary tumors. Nadofaragene is a nonreplicating adenovirus gene therapy, dosed once every 3 months, that delivers interferon  $\alpha 2b$  to urothelial cells. Outcomes from 5 years of follow-up from the phase 3 study provide patients and clinicians with insights into safety and efficacy.

**What We Found:** Kaplan-Meier–estimated high-grade recurrence–free survival at 57 months was 13% (95% CI 6.9-21.5) in the CIS cohort and 33% (95% CI 19.5-46.6) in the Ta/T1 cohort. Of note, 14/55 (25%) patients in the CIS cohort and 17/35 (49%) patients in the Ta/T1 cohort had ongoing response at either end of follow-up or at last available follow-up (Figure). Cystectomy-free survival at month 60 was 49% (95% CI 40.0-57.1); 43% (95% CI 32.2-53.7) in the CIS cohort and 59% (95% CI 43.1-71.4) in the Ta/T1 cohort. This study was unique for its mandatory 12-month end of study biopsy and its conservative approach to redosing, which was only offered to patients who achieved a complete response. There were no grade 4 or 5 adverse events.



**Figure.** Time to complete response and duration of complete response in patients with carcinoma in situ. NMIBC indicates nonmuscle-invasive bladder cancer.

**Limitations:** Detailed safety data beyond 24 months were not collected, although drug-related adverse events were captured for the full follow-up period. Longer-term cystectomy data including the final pathology for patients who underwent surgery were also not collected.

**Interpretation for Patient Care:** Nadofaragene provided patients with BCG-unresponsive NMIBC a safe and conveniently dosed treatment option, allowing for bladder preservation for nearly half of participants. Although only a minority of patients remained free of high-grade disease by the end of the follow-up period, few patients experienced clinical progression to muscle-invasive disease, and overall survival was 80% (95% CI 71.0-86.0).

## Efficacy of Intravesical Nadofaragene Firadenovec for Patients With Bacillus Calmette-Guérin–Unresponsive Nonmuscle-Invasive Bladder Cancer: 5-Year Follow-Up From a Phase 3 Trial

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**Purpose:** Nadofaragene firadenovec-vnvg is a nonreplicating adenoviral vector–based gene therapy for bacillus Calmette-Guérin (BCG)–unresponsive carcinoma in situ (CIS) with/without high-grade Ta/T1. We report outcomes following 5 years of planned follow-up.

**Materials and Methods:** This open-label phase 3 trial (NCT02773849) enrolled patients with BCG-unresponsive nonmuscle-invasive bladder cancer in 2 cohorts: CIS ± Ta/T1 (CIS; n = 107) and Ta/T1 without CIS (Ta/T1 cohort; n = 50). Patients received 75 mL ( $3 \times 10^{11}$  vp/mL) nadofaragene firadenovec intravesically once every 3 months with cystoscopy and cytology assessments, with continued treatment offered to those remaining high grade recurrence-free (HGRF).

**Results:** One hundred fifty-seven patients were enrolled from 33 US sites (n = 151 included in efficacy analyses). Median follow-up was 50.8 months (interquartile range 39.1-60.0), with 27% receiving  $\geq 5$  instillations and 7.6% receiving treatment for  $\geq 57$  months. Of patients with CIS 5.8% (95% CI 2.2-12.2) were HGRF at month 57, and 15% (95% CI 6.1-27.8) of patients with high-grade Ta/T1 were HGRF at month 57. Kaplan-Meier-estimated HGRF survival at 57 months was 13% (95% CI 6.9-21.5) and 33% (95% CI 19.5-46.6) in the CIS and Ta/T1 cohorts, respectively. Cystectomy-free survival at month 60 was 49% (95% CI 40.0-57.1): 43% (95% CI 32.2-53.7) in the CIS cohort and 59% (95% CI 43.1-71.4) in the Ta/T1 cohort. Overall survival at 60

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Dr Shore reported serving as a consultant for and receiving funding from Astellas, Dendreon, Janssen, Bayer, Myriad, MDxHealth, Tolmar, Myovant, Pfizer, EMD Serono Inc, AstraZeneca, Merck, Urogen, Guardant, Abbvie, Amgen, Bristol Myers Squibb, Boston Scientific, Clovis Oncology, Exact Imaging, FerGene, Foundation Medicine, CG Oncology, Invitae, Nymox, Propella, Sanofi, Sesen Bio, Exact Science, Pacific Edge, Cold Genes, Genesis Care, Alessa, Akido, Amgen, Arquer, Asieris, Clarity, Genentech, Guardant, Ferring Pharmaceuticals Inc, ImmunityB, Incyte, Lantheus, Lilly, Minomic, NGM, Nanogen, Novartis, Photocure, PlatformQ, Profound, Promaxo, Protara, Speciality Networks, Telix, Vaxion, Vessi, FZE Medical, Accord, ANTEV, BioProtect, Aura Biosciences, Palette Life, and Preview, and reported receiving funding from a leadership role in GenesisCare, Alessa, and Photocure, and funding related to a scientific study from Genentech. 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Dr Lerner reported serving as a consultant/advisor for Vaxion, Verity, Pfizer, Surge Therapeutics, C2i Genomics, BMS, Incyte, Protara, AstraZeneca, Gilead, Urogen, and Ferring; participating in a scientific study or trial for FKD, Viventia, Roche/Genentech, Vaxion, QED Therapeutics, Aura Biosciences, and Surge Therapeutics; holding a role in health publishing for *UpToDate* and *Bladder Cancer Journal*, and serving as a meeting participant or lecturer for grand rounds urology, *UroToday*, Dava Oncology; he also has a patent for TCGA classifier. Dr Steinberg reported membership in Clinical Trial Protocol Committees for Merck, BMS, Janssen, CG Oncology, Pfizer, PhotoCure, Fidia, Seagen, and Protara; being a past or present scientific advisor/consultant within the past 36 months for CG Oncology, PhotoCure, Merck, Taris Biomedical (Now Janssen), Fidia Pharma, Urogen, Ferring Pharmaceuticals Inc, FerGene, Bristol Myers Squibb, AstraZeneca, Pfizer, Janssen, Epivax Therapeutics, EnGene Bio, Astellas, SeaGen, Verity Pharmaceuticals, Protara, xCures, Nonagen, Nanology, Imvax, Asieris, UroViu, and Aura Biosciences; and owning equity stock/options in Epivax Therapeutics, CG Oncology, and Engene Bio. Dr Schuckman reported serving on an advisory board and receiving funding from Pacific Edge. Dr Karsh reported receiving funding related to scientific study, consultancy, and speaker roles from AbbVie, AstraZeneca, Astellas, Bayer, Bristol Myers Squibb, Cleveland Dx, Epizyme, FKD Therapies Oy, Ferring Pharmaceuticals, Janssen, OncoCell mDx, Merck, Pfizer, and Sumitomo Pharma. Dr Brown reported serving as a consultant/lecturer for and receiving funding from Astellas, Janssen, Bayer, AstraZeneca, and Merck. Dr Lotan reported serving as a consultant/advisor for and receiving funding from Pacific Edge, Photocure, AstraZeneca, Vessi Medical, Nucleix, Merck, Engene, CAPS Medical, C2i Genomics, FerGene, Abbvie, Ambu, Seattle Genetics, Verity Pharmaceuticals, Urogen, Stimit, Nanorobot, Convergent Genomics, Aura Biosciences, Nonagen, Valar Lab, Pfizer, Phinomics, CG Oncology, Virtuoso Surgical, xCures, Uroviu, On Target Lab, Promis Diagnostics, and Urossentials. Dr Lotan reported receiving funds for involvement with data monitoring and safety committee from Urogen, and disclosed nonfinancial scientific study or trial involvement with FKD, MDxHealth, and GenomeDx Biosciences Inc. Dr Inman reported receiving research funding from Profound Medical, Medtronic, Combat Medical, FKD Therapies, Genentech Roche, CG Oncology, Janssen, and Seattle Genetics, as well as funding as an advisor for Johnson & Johnson and Combat Medical. Dr Williams reported serving as a consultant/advisor for and receiving funding from Pacific Edge Diagnostics, Ferring Pharmaceuticals Inc, Olympus, Pfizer, and Astellas. Dr Williams reported receiving funds as a meeting participant or lecturer from UroGPO and for scientific study or trial involvement from Astellas, and disclosed nonfinancial scientific study or trial involvement with Janssen, Merck, Anchiano Therapeutics, AstraZeneca, Dendreon Pharmaceuticals, FKD Therapies, Genomic Health, and Pfizer. 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Dr Dinney reported creating intellectual property owned by UT/MDACC related to the use of genetic alterations as a predictive biomarker for response to Nadofaragene firadenovec, owning stock options and receiving personal compensation from CG Oncology for consulting and advisory services, and receiving research funding from NCI. No other disclosures were reported.

**Ethics Statement:** The study procedures and analyses were conducted per protocol and all protocol amendments were approved by the Institutional Review Board prior to implementation (Supplementary Material, <https://www.jurology.com>).

#### Author Contributions:

**Conception and design:** Boorjian, Kamat, Lerner, Bivalacqua, Steinberg, O'Donnell, Yla-Herttuala, Parker, Philipson, and Dinney.

**Data acquisition:** All authors.

**Data analysis and interpretation:** All authors.

**Drafting the manuscript:** Narayan, Dinney.

**Critical revision of the manuscript for scientific and factual content:** All authors.

**Statistical analysis:** Rehm.

**Supervision:** All authors.

**Data Availability:** The data that support the findings of this study are available from Ferring Pharmaceuticals Ltd but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are, however, available from the authors upon reasonable request and with permission of Ferring Pharmaceuticals Ltd.

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months was 80% (71.0, 86.0): 76% (64.6-84.5) and 86% (70.9-93.5) in the CIS and Ta/T1 cohorts, respectively. Only 5 patients (4 with CIS and 1 with Ta/T1) experienced clinical progression to muscle-invasive disease.

**Conclusions:** At 60 months, nadofaragene firadenovec-vncg allowed bladder preservation in nearly half of the patients and proved to be a safe option for BCG-unresponsive nonmuscle-invasive bladder cancer.

**Key Words:** bladder cancer, nonmuscle invasive bladder cancer, intravesical instillation, gene therapy, BCG-unresponsive bladder cancer

NONMUSCLE-INVASIVE bladder cancer (NMIBC) represents the majority of new diagnoses of bladder cancer, and bacillus Calmette-Guérin (BCG) therapy remains the most effective intravesical therapy for patients with high-risk disease.<sup>1</sup> Despite this, over half of patients experience recurrence and progression, and many develop BCG-unresponsive disease, a clinical condition that remains challenging to treat.<sup>2,3</sup> Although radical cystectomy offers definitive cancer treatment in this setting, many patients desire bladder-sparing options.

Several novel agents have been or are currently undergoing investigation as potential bladder sparing options, and in December 2022 the US Food and Drug Administration (FDA) approved nadofaragene firadenovec (nadofaragene) for patients with BCG-unresponsive carcinoma in situ (CIS) with or without high-grade Ta/T1 NMIBC. Nadofaragene (rAd-interferon [IFN] $\alpha$ /Syn3) consists of rAd-IFN $\alpha$ , a nonreplicating adenovirus vector-based gene therapy that delivers a copy of the human IFN $\alpha$ 2b to urothelial cells.<sup>4-6</sup> The drug formulation also contains Syn3, a polyamide surfactant that enhances the viral transduction of the urothelium.<sup>7</sup> Recombinant Ad-IFN $\alpha$  gene therapy results in local IFN $\alpha$ -2b production and has been demonstrated to induce tumor regression in preclinical studies.<sup>4-6</sup> We previously reported 12 month follow-up data from the phase 3 study (NCT02773849), in which 53.4% of patients with BCG-unresponsive CIS experienced a complete response (CR) by 3 months, with this response maintained in 45% of responders at 12 months.<sup>8</sup> We report the final long-term efficacy and safety outcomes following 5 years of follow-up, and hypothesized that nadofaragene would be associated with low risk of progression while allowing a significant portion of patients to retain their bladder.

## METHODS

### Study Design and Participants

This was a single-arm, open-label, repeat-dose, phase 3 clinical study conducted across 33 sites in the US, with the protocol designed by the Society of Urologic Oncology Clinical Trials Consortium. Patients who met the definition of BCG-unresponsive disease according to the 2018 FDA Guidance for Industry were included<sup>9</sup> (Supplementary Table, <https://www.jurology.com>). Patients

were enrolled into 2 cohorts: the CIS  $\pm$  Ta/T1 cohort comprised of patients with CIS with or without concomitant high-grade Ta or T1 NMIBC (Ta/T1) at diagnosis, and the Ta/T1 cohort comprised patients with Ta or T1 tumors without concomitant CIS. Full inclusion and exclusion criteria including the study protocol have been previously reported.<sup>8</sup>

The study protocol was approved by an Institutional Review Board for each center (Supplementary Material, <https://www.jurology.com>) before accrual and conducted in accordance with the Declaration of Helsinki, in compliance with Good Clinical Practice Guidelines. The study procedures and analyses were conducted per protocol and all protocol amendments were approved by the Institutional Review Board prior to implementation. All patients provided written informed consent prior to enrollment.

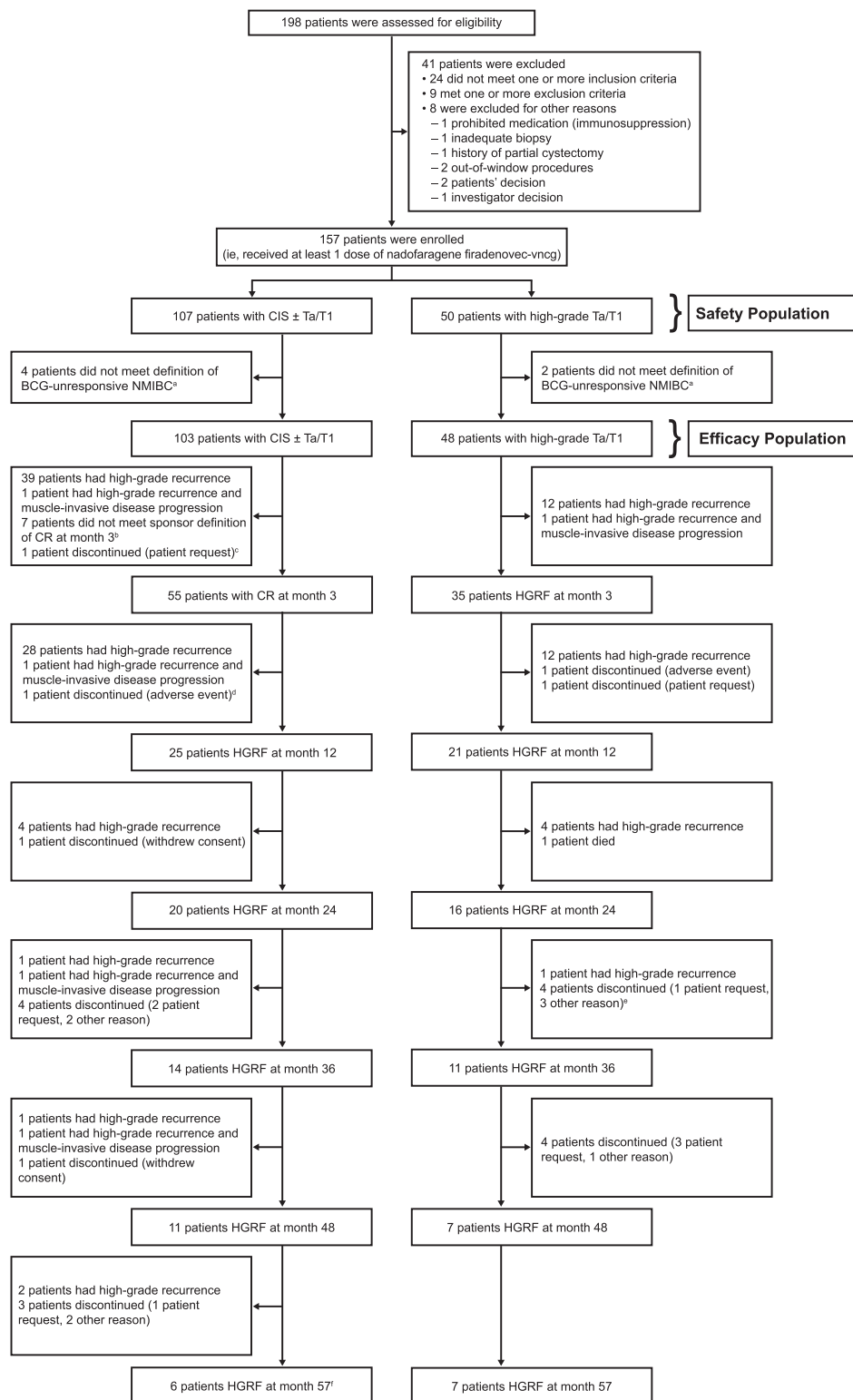
### Procedures

Patients received nadofaragene 75 mL ( $3 \times 10^{11}$  vp/mL) via intravesical administration through a urinary catheter. The dose and administration regimen were based on results from a previous phase 2 study.<sup>10</sup> All patients were evaluated for recurrence with urine cytology and cystoscopy, with biopsies performed for cause, at efficacy assessment visits once every 3 months. In the absence of high-grade recurrence, administration was repeated at month 3 (day 90), month 6 (day 180), and month 9 (day 270). Patients demonstrating recurrence of high-grade disease at any time were removed from the treatment schedule. All patients were required to undergo a biopsy of 5 sites (dome, trigone, right and left lateral wall, posterior wall) at 12 months after initial treatment.

Following the initial 12-month treatment period, patients entered a 4-year follow-up monitoring period, irrespective of whether nadofaragene treatment was continued. Patients who had high-grade recurrence were withdrawn from treatment and had follow-up data for survival and cystectomy status collected annually for up to 5 years. Those without evidence of high-grade recurrence were allowed to continue treatment once every 3 months at the discretion of their physician.

### Outcomes

The primary objective of the original study was to evaluate the CR rate in the CIS  $\pm$  Ta/T1 cohort at any time within 12 months after first instillation of nadofaragene. CR was defined as a negative urine cytology and cystoscopy, or negative biopsy if performed for cause and/or at 12 months. We report the secondary end points including overall survival (OS), durability of CR, incidence of high-grade recurrence-free (HGRF) survival (at month 12, 24,



**Figure 1.** Patient disposition (CONSORT [Consolidated Standards of Reporting Trials] diagram). BCG indicates bacillus Calmette-Guérin; CIS, carcinoma in situ; CR, complete response; HGRF, high-grade recurrence-free; NMIBC, nonmuscle-invasive bladder cancer. <sup>a</sup>Postenrollment review of medical records. <sup>b</sup>As defined in the final statistical analysis plan. <sup>c</sup>This patient did not have any posttreatment response assessment. <sup>d</sup>This patient was later recorded as having recurrence of high-grade disease at month 18. <sup>e</sup>Of the 3 patients who discontinued for other reasons, all 3 received last treatment at month 9. <sup>f</sup>One patient was subsequently reported to have high-grade recurrence at month 63.

36, 48, and 57), durability of HGRF survival, incidence of cystectomy (at month 12, and 2 and 5 years), cystectomy-free survival (CFS), and safety of nadofaragene during the long-term follow-up period. OS is defined as the time from first dose of nadofaragene to death. If death does not occur patients are censored at the last time known to be alive. Durability of CR is defined as the time from first observed CR to documented high-grade tumor recurrence, disease progression, or death from any cause. Patients with no events are censored at the last disease assessment showing no recurrence of high-grade tumors or progression. HGRF survival is defined as participants who are alive and in whom cystoscopy, cytology, and biopsy examination (if clinically indicated or mandated) shows either no evidence of recurrent CIS, Ta, or T1 lesions or progression, or shows evidence of a Ta or T1 lesions which are evaluated as low-grade. Durability of HGRF survival is time from first dose of nadofaragene to recurrence of high-grade tumors, disease progression, or death. Censoring is performed as described for durability of CR. CFS is defined as time from first dose of nadofaragene to cystectomy or death from any cause. Any patient without a CFS event is censored at the time of last known status for cystectomy. Final outcomes from the 60-month follow-up are reported.

### Statistical Analysis

Statistical considerations, including assumptions made for sample size calculations for the original study, have been previously reported.<sup>8</sup> The safety analysis set was defined as all patients who received at least 1 dose of nadofaragene and was used for safety analyses. The efficacy analysis set was defined as all patients in the safety analysis set who met the strict definition of BCG-unresponsive NMIBC (Figure 1) and was used for efficacy analyses. The proportions of CIS patients achieving CR and of patients with HGRF survival at different timepoints are presented with a 2-sided 95% Clopper-Pearson confidence interval. Patients with missing data were considered nonresponders. OS, CFS, durability of CR and HGRF survival as time-to-event end points were evaluated using the Kaplan-Meier (KM) method. Missing data for time-to-event end points were handled by non-informative censoring. Descriptive statistics were used to summarize the demographic, baseline, and safety data. Statistical analyses were done with SAS version 9.4.

## RESULTS

Between September 2016 and May 2019, 198 patients were assessed for eligibility, and 157 patients were enrolled and received at least 1 dose of nadofaragene (Table 1). Of these patients, 107 (68%) were diagnosed with CIS ± Ta/T1, while 50 (32%) had Ta/T1 disease alone. The efficacy analysis set included 151 patients (103 in the CIS ± Ta/T1 cohort and 48 in the Ta/T1 cohort), with 6 patients excluded (4 in the CIS ± Ta/T1 cohort and 2 in the Ta/T1 cohort) because it was determined that they did not meet the protocol definition for BCG-unresponsive NMIBC after receiving their first dose of nadofaragene. The

**Table 1. Patient Characteristics at Baseline**

	CIS (n = 107)	High-grade Ta or T1 cohort (n = 50)
Age at baseline, median (IQR), y	72 (66-77)	71 (64-78)
Male sex, No. (%)	95 (89)	34 (68)
Race, No. (%)		
White	99 (93)	47 (94)
Black or African American	6 (5.6)	2 (4.0)
Asian	2 (1.9)	1 (2.0)
Time from initial diagnosis of bladder cancer, median (IQR), mo	20 (13-35)	15 (12-22)
Previous courses of BCG administered, No. (%) <sup>a</sup>		
1	1 (0.9)	5 (10)
2	45 (42)	28 (56)
3	28 (26)	12 (24)
4	12 (11)	2 (4.0)
≥5	21 (20)	3 (6.0)
Stage at baseline, No. (%)		
CIS only	81 (76)	NA
Ta	NA	35 (70)
CIS + Ta	21 (20)	NA
T1	NA	15 (30)
CIS + T1	5 (4.7)	NA
ECOG performance status, No. (%)		
0	97 (91)	43 (86)
1	7 (6.5)	6 (12)
2	3 (2.8)	1 (2.0)

Abbreviations: BCG, bacillus Calmette-Guérin; CIS, carcinoma in situ; ECOG, Eastern Cooperative Oncology Group; IQR, interquartile range; NA, not applicable.

<sup>a</sup> A course of BCG was defined as at least 5 of 6 initial induction BCG doses plus at least 2 of 3 maintenance BCG doses, or at least 2 of 6 instillations of a second induction course in which maintenance BCG is not given.

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safety analysis set, for which data were reported previously, included all 157 patients who received at least 1 dose of nadofaragene.<sup>8</sup>

Among all enrolled patients, 63 (40%) patients completed the 12-month treatment period, 42 of these continued treatment beyond 12 months, 31 continued treatments at or after 24 months, and 12 received treatment for at least 57 months. Median follow-up was 50.8 months (interquartile range [IQR] 39.1-60.0). The median exposure time to nadofaragene was 3.4 months (IQR 0-12.9), while the median number of instillations was 2 (IQR 1-5), with 42 patients (27%) receiving 5 or more instillations. The primary reason for discontinuation of treatment was disease recurrence; 120 of 146 discontinuations were attributed to disease recurrence by the end of the full follow-up period. Ninety-five patients (61%) in the overall population completed up to 5 years of follow-up.

### Efficacy Outcomes

The 12-month efficacy analysis was reported previously,<sup>8</sup> with 53.4% of patients (95% CI 43.3-63.3) in the CIS ± Ta/T1 cohort achieving the primary outcome of a CR; all CRs were noted at 3 months (Table 2). At the end of 5 years of follow-up, 118



**Table 2.** Complete Response, High-Grade Recurrence-Free Survival, and Cystectomy-Free Survival in the Efficacy Analysis Set

	CIS (n = 103)		High-grade Ta or T1 cohort (n = 48)		All patients (n = 151)	
Patients with complete response <sup>a</sup> or HGRF survival <sup>b</sup> at scheduled mo <sup>c</sup> 3 efficacy evaluation visit, No. (% [95% CI])	55	(53.4 [43.4-63.3])	35	(72.9 [58.2-84.7])	90	(59.6 [51.3-67.5])
Duration of HGRF survival, (95% CI), <sup>d</sup> mo	5.9	(3.4-8.3)	12.4	(6.7-20.3)	7.3	(5.7-11.9)
Patients who were free from high-grade recurrence <sup>e</sup> at mo, No. (% [95% CI])						
12	25	(24 [16.4-33.7])	21	(44 [29.5-58.8])	46	(30 [23.2-38.5])
24	20	(19 [12.3-28.4])	16	(33 [20.4-48.4])	36	(24 [17.3-31.4])
36	14	(14 [7.6-21.8])	11	(23 [12.0-37.3])	25	(17 [11.0-23.5])
48	11	(11 [5.5-18.3])	7	(15 [6.1-27.8])	18	(12 [7.2-18.2])
57	6	(5.8 [2.2-12.2])	7	(15 [6.1-27.8])	13	(8.6 [4.7-14.3])
Cystectomy-free survival rate, % (95% CI) <sup>e</sup>						
12 mo	73	(62.9-80.5)	83	(69.2-91.2)	76	(68.4-82.3)
24 mo	63	(53.1-72.1)	72	(57.2-83.0)	66	(58.1-73.4)
36 mo	54	(43.5-63.2)	64	(48.1-75.6)	57	(48.5-64.7)
48 mo	49	(38.6-58.7)	59	(43.1-71.4)	52	(43.6-60.1)
60 mo	43	(32.2-53.7)	59	(43.1-71.4)	49	(40.0-57.1)

Abbreviations: CIS, carcinoma in situ; HGRF, high-grade recurrence-free.

<sup>a</sup> Patients in the CIS cohort.

<sup>b</sup> Patients in the high-grade Ta or T1 cohort.

<sup>c</sup> Month reflects the nominal value of the scheduled efficacy evaluation visit.

<sup>d</sup> Kaplan-Meier estimate of median duration from first dose of nadofaragene firadenovec.

<sup>e</sup> Kaplan-Meier estimated rates of cystectomy-free survival.

patients (78%) had recurrence of high-grade disease: 88 patients (85%) in the CIS cohort and 30 patients (63%) in the Ta/T1 disease cohort. Only 5 patients (3.3%) had a documented clinical muscle-invasive disease progression, and 1 patient (0.7%) died before recurrence (metastatic lung cancer). A total of 31 patients (21%) remained recurrence-free (median follow-up time for HGRF survival was 45.7 months) and 1 patient (0.7%) did not have any posttreatment disease assessment (discontinued treatment per patient request). HGRF survival was 5.8% (95% CI 2.2-12.2) in the CIS cohort and 15% (95% CI 6.1-27.8) in the Ta or T1 cohorts by the end of the 5-year follow-up period (Table 2). At 12 months, 24% (95% CI 16.4-33.7) of patients were free from high-grade recurrence in the CIS cohort. At 24 and 36 months, 19% (95% CI 12.3-28.4) and 14% (95% CI 7.6-21.8) were free from high-grade recurrence, respectively. In the Ta/T1 cohort, at 12 months, 44% (95% CI 29.5-58.8) of patients were free from high-grade recurrence, while at 24 and 36 months, 33% (95% CI 20.4-48.4) and 23% (95% CI 12.0-37.3) were free from high-grade recurrence. The median duration of HGRF survival was 7.3 (95% CI 5.7-11.9) months in the overall cohort, 5.9 months (95% CI 3.4-8.3) in the CIS cohort, and 12.4 months (95% CI 6.7-20.3) in the Ta/T1 cohort (Table 2). Nine patients (8.7%) with CIS and 10 (21%) with Ta/T1 disease discontinued treatment with an ongoing response at last follow-up for HGRF survival. The KM-estimated probability of remaining HGRF in the CIS cohort for at least 57 months was 13% (95% CI 6.9-21.5) and 33% (95% CI 19.5-46.6) for patients in the Ta/T1 cohort (Figure 2, B and Figure 3, A).

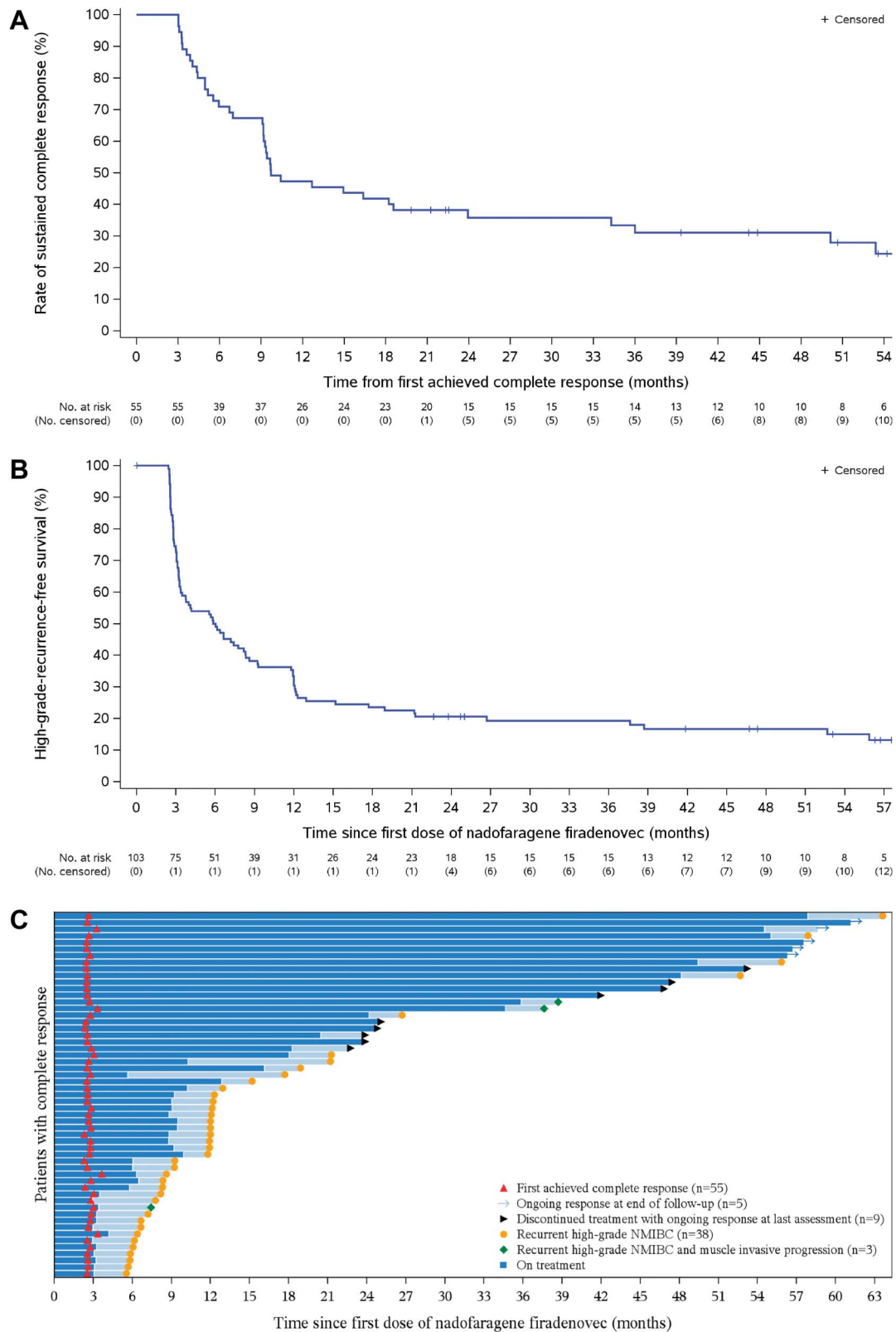
### Patients Achieving a CR at 3 Months

Among the 55 patients with CIS who achieved an initial CR, the median duration of CR was 9.7 months (95% CI 9.2-24.0, Figure 2, A and C). In this group of responding patients, HGRF survival was maintained in 25 (45%) at month 12, when all patients underwent a mandatory biopsy regardless of cystoscopy findings (Figure 2, C). At 24 months, 20 patients (36%) remained HGRF, while 14 (25%) were HGRF at 36 months, 11 (20%) at 48 months, and 6 (11%) at 57 months (Figure 2, C).

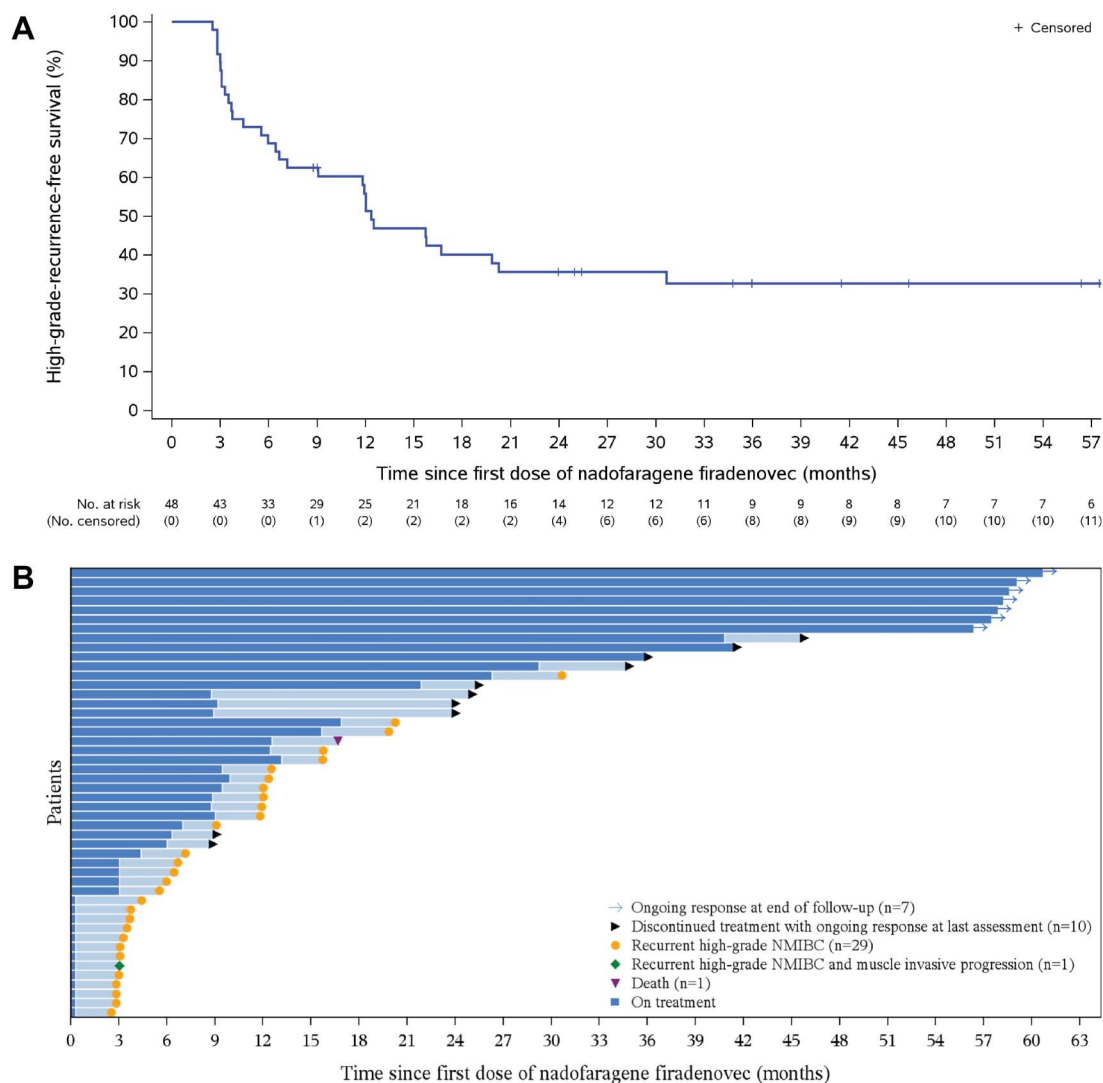
Among the 35 patients in the Ta/T1 cohort who were HGRF at month 3, 21 (60%) remained HGRF at month 12. At 24 months, 16 patients (46%) remained HGRF, while 11 (31%) were HGRF at 36 months, 7 (20%) at 48 months, and 7 (20%) at 57 months (Figure 3, B).

### Bladder Preservation

A key patient-centered goal is bladder preservation. Fifty-eight patients underwent radical cystectomy during the follow-up period: 34 (23%) within 12 months after the first dose, 45 (30%) within 2 years after the first dose, and 56 (37%) within 5 years after the first dose. The median duration of CFS for the overall study population was 58 months (95% CI 33-not estimable [NE]) and 48 months (95% CI 27-61) for patients in the CIS cohort (Figure 4, A); the median was not reached at end of study (95% CI 35-NE) for the Ta/T1 cohort (Figure 4, B). The KM-estimated CFS rate for the overall study population at month 60 was 49% (95% CI 40.0-57.1): 43% (95% CI 32.2-53.7) in the CIS cohort and 59% (95% CI 43.1-71.4) in the Ta/T1 cohort (Table 2).



**Figure 2.** A, Kaplan-Meier estimates of durability of complete response in patients with carcinoma in situ, among patients who achieved complete response. B, Kaplan-Meier estimates of durability of high-grade recurrence-free survival in patients with carcinoma in situ, all patients. C, Time to complete response and duration of complete response in patients with carcinoma in situ. NMIBC indicates nonmuscle-invasive bladder cancer.



**Figure 3.** A, Kaplan-Meier estimates of durability of high-grade recurrence-free survival in patients with high-grade Ta/T1 disease. B, Duration of high-grade recurrence-free survival in patients with high-grade Ta/T1 disease. NMIBC indicates nonmuscle-invasive bladder cancer.

## OS

The KM-estimated OS rate for the overall study population at month 60 was 80% (95% CI 71.0-86.0): 76% (95% CI 64.6-84.5) in the CIS cohort and 86% (95% CI 70.9-93.5) in the Ta/T1 cohort (Figure 5). The median duration of OS was not reached for the overall study population and for both cohorts.

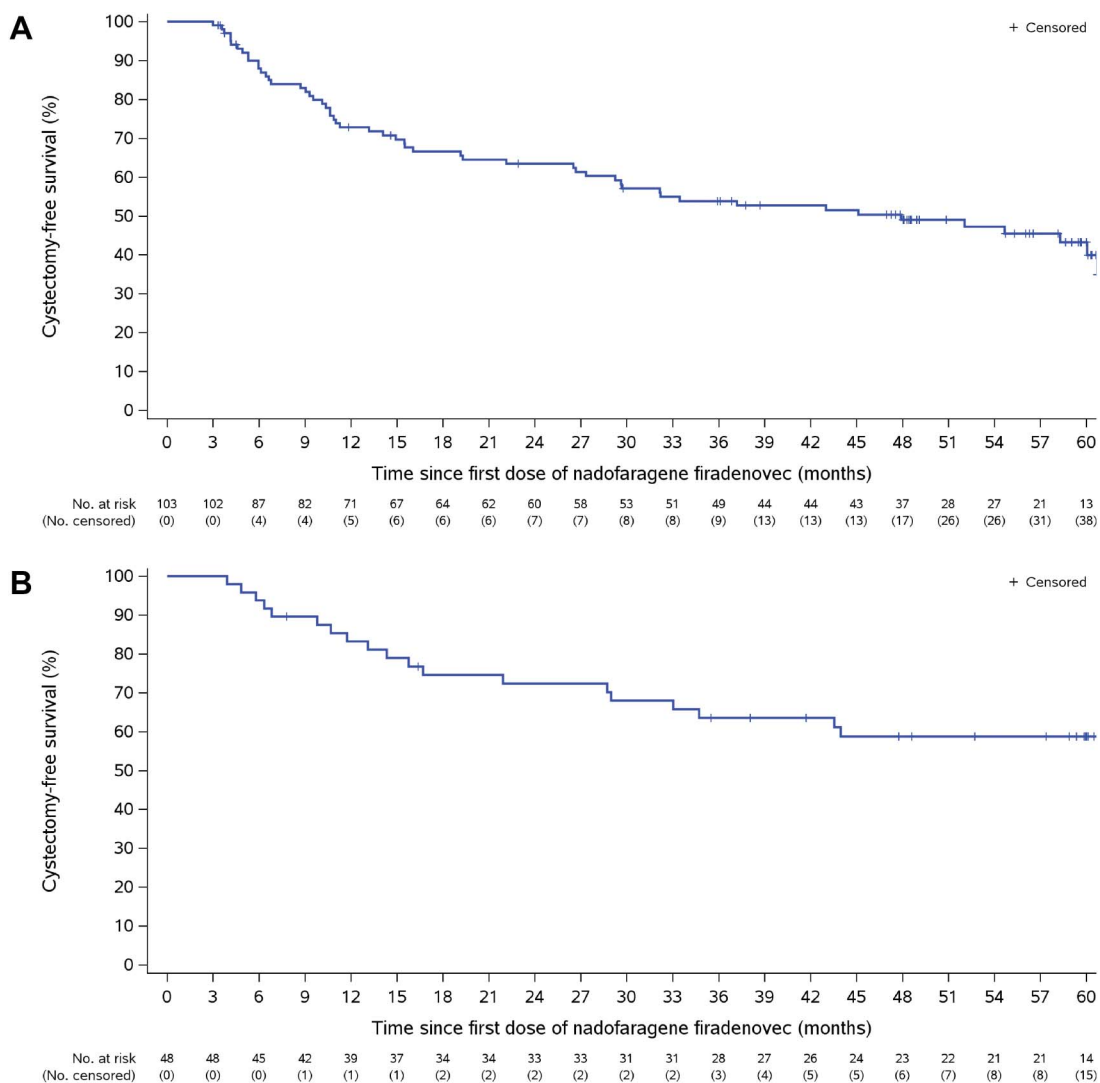
## Safety Outcomes

Details regarding adverse events were previously reported, and no new safety signals were seen with long-term follow-up.<sup>8</sup> The most common study drug related treatment-emergent adverse events were discharge around the catheter during instillation, fatigue, bladder spasms, and micturition urgency (Table 3). Most adverse events were grades 1 or 2

(66%), with 3.8% of patients reporting grade 3 events and no patients experiencing grades 4 or 5 study-drug related adverse events.

## DISCUSSION

With 5 years of follow-up data, the present study demonstrates that nadofaragene provided nearly half of participants in the CIS cohort and two-thirds of those in the Ta/T1 cohort with bladder preservation at 60 months, representing a safe treatment option for patients with BCG-unresponsive NMIBC. Furthermore, no new safety signals emerged with long-term follow-up, and no deaths were attributed to the study drug, which is noteworthy given that it is a novel, first-in-class intravesical gene therapy. Clinical progression to muscle invasion was rare with 5 patients having documented muscle-invasive

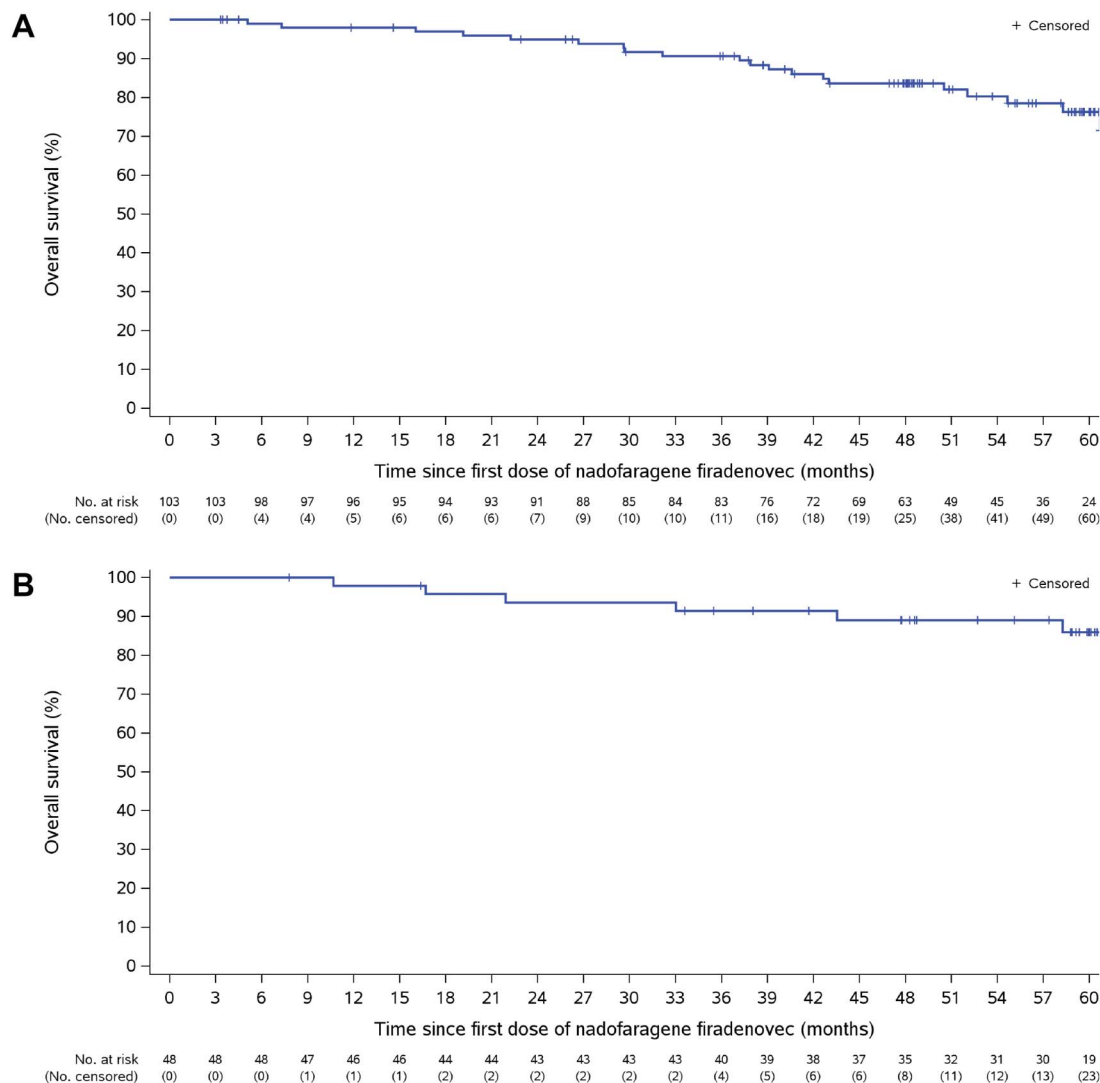


**Figure 4.** A, Kaplan-Meier estimates of cystectomy-free survival in patients with carcinoma in situ. B, Kaplan-Meier estimates of cystectomy-free survival in patients with high-grade Ta/T1 disease.

disease progression over the 5-year follow-up period. Moreover, the median duration of CFS was 58 months (95% CI 33-NE), including 48 months (95% CI 27-60) for patients in the CIS cohort, providing reasonable bladder preservation for patients who were unwilling or unable to undergo radical cystectomy.

BCG-unresponsive NMIBC remains a challenging disease state with limited therapeutic options. Our long-term follow-up of 5 years further underscores this, with only 5.8% of all patients with CIS and 11% of those who achieved a CR at 3 months remaining HGRF at 5 years. Similarly, among the high-grade Ta/T1-only cohort, only 15% of all patients and 20% of those who HGRF at 3 months were HGRF by the end of the follow-up period. Nevertheless, nadofaragene offers patients a convenient dosing schedule, with treatments administered once every 3 months.

Agents currently approved by the FDA for use in BCG-unresponsive NMIBC include valrubicin, pembrolizumab, and nadofaragene. Valrubicin demonstrated a CR of 21% in patients with BCG-refractory CIS; however, this trial was conducted before a standardized definition for BCG-unresponsive disease.<sup>11,12</sup> Pembrolizumab was studied in KEYNOTE-057, with 39 participants (41%) with BCG-unresponsive CIS achieving a CR at 3 months, but nearly 22% of patients experienced immune-related AEs.<sup>13</sup> Other intravesical therapies that have been investigated include gemcitabine and docetaxel monotherapy,<sup>14,15</sup> combinations including gemcitabine/mitomycin and gemcitabine/docetaxel,<sup>16</sup> and nab-paclitaxel.<sup>17</sup> Combinations with immunotherapy, such as BCG ± atezolizumab, have also been investigated.<sup>18</sup> Additionally, the TAR-200 device, a targeted intravesical drug delivery system of controlled-release gemcitabine,



**Figure 5.** A, Kaplan-Meier estimates of overall survival in patients with carcinoma in situ. B, Kaplan-Meier estimates of overall survival in patients with high-grade Ta/T1 disease.

**Table 3.** Study Drug-Related Treatment-Emergent Adverse Events in Safety Population out to 60 Months (n = 157)

	Grade 1 or 2 No. (%)	Grade 3 No. (%)	Grade 4 or 5 No. (%)
Patients with study drug-related adverse events <sup>a</sup>	104	6	0
Types of events			
Discharge around the catheter during instillation	39 (25)	0	0
Fatigue	31 (20)	0	0
Bladder spasm	25 (16)	1 (0.6)	0
Micturition urgency	23 (15)	2 (1.3)	0
Chills	18 (11)	0	0
Dysuria	19 (12)	0	0
Pyrexia	16 (10)	0	0
Syncope	0 (0.0)	1 (0.6)	0
Hypertension	2 (1.3)	1 (0.6)	0
Urinary incontinence	6 (3.8)	1 (0.6)	0

<sup>a</sup> Events occurring in at least 10% of all treated patients during the study period.

was shown to have a CR rate of 76.7% in evaluable patients with BCG-unresponsive NMIBC with CIS (n = 23), as part of early results from the phase 2b SunRISe-1 trial.<sup>19</sup> Cretostimogene grenadenorepvec, an intravesical replicating serotype 5 adenovirus that expresses GM-CSF, demonstrated a 68.2% CR rate at 3 months in evaluable patients with BCG-unresponsive NMIBC as part of the BOND-003 interim results,<sup>20</sup> and the QUILT-3.032 study was conducted to investigate an interleukin-15 superagonist, nogapendekin alfa inbakicept (NAI or N-803), which, when combined with BCG, offered a CR rate of 55% at 3 months with BCG-unresponsive CIS alone.<sup>21</sup> Of note, many of the aforementioned agents have been investigated with either repeat treatment allowed or as combination therapies with other agents, making



direct comparisons difficult. The current study provides the longest-term follow-up efficacy data to date.

Strengths of this study include the majority of patients (61%) being able to complete the full follow-up period. Mandated bladder biopsies at 12 months also helped to confirm CR, eliminating investigator bias. There are several limitations to this study, however, including the lack of central pathology review and the fact that initial responses were based on cystoscopy and cytology results, which can be subjective. However, we believe that this approach confers real-world generalizability to these data, in which subjective cystoscopic and cytologic assessments are part of standard-of-care practice. Additional limitations include the absence of detailed safety data beyond the 24 months of follow-up period, after which only drug-related AEs were captured, the absence of longer-term cystectomy data including the

final pathology for patients who underwent cystectomy over the 5-year period, as well as lack of information on what other treatments patients who recurred may have received.

In conclusion, although long-term efficacy was limited, future investigation will focus on retreatment options for patients who recur, combination therapies as well as biomarker-directed strategies.<sup>22</sup> The safety profile and convenient delivery schedule, as well as the significant number of participants were able to preserve their bladder, offers patients with this historically difficult-to-treat disease state an additional treatment option to consider.

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