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Intravesical nadofaragene firadenovec gene therapy for BCG-unresponsive non-muscle-invasive bladder cancer: a single-arm, open-label, repeat-dose clinical trial

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Contributors

SAB, AMK, SPL, TJB, MAO, GDS, AB, SY-H, NRP, RC, RP, and CPND conceived of and designed the trial. FPT provided statistical advice. DS served as a resource for participating investigators. SAB, MA, BRK, NDS, LGG, AMK, TJB, JSM, SPL, JEB, MP, PLC, GDS, AKS, TMD, RSS, JM, BRL, TJG, GBra, LIK, MEW, GBro, DC, AL, YL, TK, BAI, MBW, MSC, KAK, GLA, AIS, MAO, DS, FPT, RC, RP, VMN, SY-H, and NRP provided study materials and enrolled patients, and collected and assembled study data. SAB, MA, BRK, NDS, LGG, AMK, TJB, JSM, SPL, JEB, MP, PLC, GDS, AKS, TMD, RSS, JM, BRL, TJG, GBra, LIK, MEW, GBro, DC, AL, YL, TK, BAI, MBW, MSC, KAK, GLA, AIS, MAO, DS, FPT, RC, RP, VMN, SY-H, NRP, and CPND were involved in data analysis and interpretation and wrote the manuscript. All authors reviewed and approved of the manuscript before submission.

Declaration of interests

SAB reports consulting fees and personal fees from Ferring, FerGene, Sanofi, and ArTara. MA reports personal fees from Ferring. BRK reports clinical trial funds from FKD; clinical trial support from BMS, Merck, and Photocure; and consulting fees and personal fees from Ferring, Convergent Genomics, Boston Scientific, and Francis Medical. NDS has participated in research and consulting for Amgen, Astellas, AstraZeneca, Bayer, Dendreon, Ferring, Janssen, Merck, Pfizer, Sanofi-Genzyme, Tolmar, BMS, Myovant, and Nymox. LGG reports personal fees from Ferring (advisory board) and a grant from the NRG Radiation Therapy Oncology Group. LGG also reports pending patents to Thomas Jefferson University for shed tumour cells detection. AMK reports advisory board work, consulting work, or personal fees from Merck, BMS, Eisai, Arquer, MDx Health, Photocure, AstraZeneca, IBCG, TMC Innovation, Theralase, BioClin Therapeutics, FKD, Cepheid, Medac, Asieris, Pfizer, Abbott Molecular, US Biotest, Ferring, Imagin, Cold Genesys, Roviant, Sessen Bio, CEC Oncology, and Nucleix, and has a joint pending patent to University of Texas/MD Anderson Cancer Center for a CyPRIT-Cytokine Panel for Response to Intravesical Immunotherapy. TJB reports personal fees and consulting work from Ferring and Photocure. SPL has received grant funding from FKD, Vaxiion, UroGen, Endo, and Vivential; consulting fees and personal fees from UroGen, Vaxiion, Merck, Pfizer, FerGene, Verity, QED, mIR Scientific, Genentech, UroToday, Dava Oncology, and Nucleix; compensation for his editorial work from the Bladder Cancer Research Journal and UpToDate; and has a patent pending for TCGA Expression Subtype Single Patient Classifier. GDS reports personal fees in his role as scientific adviser for FKD, Merck, CG Oncology, Ferring, BMS, Janssen, Photocure, Urogen, Seattle Genetics, Aduro, Pfizer, Engene Bio, and AbbVie. AKS reports consulting work for Photocure, Merck, and FerGene, and personal fees from FKD. RSS reports personal fees from and consulting work for FKD, Ferring, Merck, and MDx Health. LIK reports personal fees from and consulting work for Urogen, AstraZeneca, Ferring, Vaxiion, and Merck, and clinical trials support for Exact Sciences, FKD, GenomeDx, Janssen, Merck, QED, Urogen, Vaxiion, Nucleix, Genetech/Roche, and Ferring. GBro reports consulting, lecturing, and adviser fees from Astellas, Janssen, Bayer, and UroGPO. YL reports grants from FKD, Anchiano, Storz, Abbott, Pacific Edge, Cepheid, MDxHealth, and Decipher, and personal fees from FerGene, Merck, Ferring Research, AbbVie, Photocure, Urogen, Synergo, CAPs Medical, and Vessi. BAI reports receiving clinical trial grants from FKD, Genentech, Dendreon, Taris Biomedical, Urogen, Combat Medical, Anchiano, Nucleix, and Abbott; and personal fees from Combat Medical, Nucleix, and Ferring. MBW reports consulting work for Pacific Edge Diagnostics, Ferring, Olympus, Pfizer, and Astellas; and research for FKD, Astellas, Janssen, Merck, Anchiano, Astra Zeneca, and Dendreon. MSC reports grants and personal fees from MDX Health; personal fees from Williams, Hall & Latherow, Myovant Sciences, Bayer, Sturgill, Turner, Barker & Mahoney, Boehl Stopher & Graves, Merck, Astellas, Janssen, and La Cava & Jacobson; and grants from Bayer and Janssen Biotech. GLA reports a research grant from FKD. AIS reports personal fees from Photocure and Genentech. MAO reports grant support from Abbott Molecular, consulting work for Fidia, Theralese, Urogen, and Vaxiion, and is an investigator for Medical Enterprises and Photocure. FPT reports consulting work for 4D, Acacia, Algipharma, Altimmune, Ascension, AstraZeneca, Ateria, Athersys, Biocompatibles, Camallergy, Canbex, CellAct, Chimerix, Clinigen, Diagnostics in the Real World, Diurnal, FKD Therapies Oy, Genexine, Gensight, Hubro, Imcyse, Invex, Italfarmaco, Mallinckrodt, Medicinova, MeiraGTX, Mundipharma, Mylan, Opsona, Optibio, Origin Sciences, Orphazyme, Phoenix, ReViral, Therakind, Trizell, and Vaxxas. RC is an employee of Trizell, which received fees from FKD. AB and SY-H received personal fees from FKD. NRP received personal fees from FKD and Trizell. CPND acknowledges using shared resources covered by the Cancer Center Support Grant funding from the National Institutes for Health/ational Cancer Institute (award number P30CA016672) at MD Anderson Cancer Center, has received grant and personal fees from FKD, and is a creator of intellectual property owned by UT/MDACC related to the use of genetic alterations as a predictive biomarker for response to nadofaragene firadenovec. All other authors declare no competing interests.

Data sharing

The study protocol is available in the appendix (p 9). Individual participant data that underlie the results reported in this Article, after de-identification (text, tables, figures, and appendices), can be made available to investigators for research purposes on a case-by-case basis following the time of this publication. Requests for access to data should be addressed to the corresponding author for consideration.

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Summary

Background—BCG is the most effective therapy for high-risk non-muscle-invasive bladder cancer. Nadofaragene firadenovec (also known as rAd-IFNa/Syn3) is a replication-deficient recombinant adenovirus that delivers human interferon alfa-2b cDNA into the bladder epithelium, and a novel intravesical therapy for BCG-unresponsive non-muscle-invasive bladder cancer. We aimed to evaluate its efficacy in patients with BCG-unresponsive non-muscle-invasive bladder cancer.

Methods—In this phase 3, multicentre, open-label, repeat-dose study done in 33 centres (hospitals and clinics) in the USA, we recruited patients aged 18 years or older, with BCG-unresponsive non-muscle-invasive bladder cancer and an Eastern Cooperative Oncology Group status of 2 or less. Patients were excluded if they had upper urinary tract disease, urothelial carcinoma within the prostatic urethra, lymphovascular invasion, micropapillary disease, or hydronephrosis. Eligible patients received a single intravesical 75 mL dose of nadofaragene firadenovec (3×10^{11} viral particles per mL). Repeat dosing at months 3, 6, and 9 was done in the absence of high-grade recurrence. The primary endpoint was complete response at any time in patients with carcinoma in situ (with or without a high-grade Ta or T1 tumour). The null hypothesis specified a complete response rate of less than 27% in this cohort. Efficacy analyses were done on the per-protocol population, to include only patients strictly meeting the BCG-unresponsive definition. Safety analyses were done in all patients who received at least one dose of treatment. The study is ongoing, with a planned 4-year treatment and monitoring phase. This study is registered with ClinicalTrials.gov, NCT02773849.

Findings—Between Sept 19, 2016, and May 24, 2019, 198 patients were assessed for eligibility. 41 patients were excluded, and 157 were enrolled and received at least one dose of the study drug. Six patients did not meet the definition of BCG-unresponsive non-muscle-invasive bladder cancer and were therefore excluded from efficacy analyses; the remaining 151 patients were included in the per-protocol efficacy analyses. 55 (53·4%) of 103 patients with carcinoma in situ (with or without a high-grade Ta or T1 tumour) had a complete response within 3 months of the first dose and this response was maintained in 25 (45·5%) of 55 patients at 12 months. Micturition urgency was the most common grade 3–4 study drug-related adverse event (two [1%] of 157 patients, both grade 3), and there were no treatment-related deaths.

Interpretation—Intravesical nadofaragene firadenovec was efficacious, with a favourable benefit:risk ratio, in patients with BCG-unresponsive non-muscle-invasive bladder cancer. This represents a novel treatment option in a therapeutically challenging disease state.

Funding—FKD Therapies Oy.

Introduction

BCG is the most effective intravesical therapy for patients with high-risk non-muscle-invasive bladder cancer.[1] Although 80% of patients have an initial complete response to induction BCG, more than half of patients have recurrence and progression within the first year, and many will develop BCG-unresponsive disease.[2–5]

Radical cystectomy is the most definitive cancer treatment in this setting, but it is associated with high perioperative morbidity and many patients are unwilling or unable to undergo the procedure. Several agents have been evaluated as intravesical therapies after BCG, but none has provided a robust and durable response, and the development of an effective, safe, and durable intravesical treatment remains a critical unmet clinical need for patients who want to avoid radical cystectomy or the systemic side-effects of immunotherapy.[6]

Intravesical recombinant interferon alfa-2b protein is well tolerated and has shown clinical effectiveness for patients with non-muscle-invasive bladder cancer after BCG.[7] Unfortunately, responses were not durable,[8] probably in part due to the short drug exposure time of 1–2 h.[7] Intravesical interferon alfa gene delivery offers a novel opportunity for local management of non-muscle-invasive bladder cancer by greatly increasing the duration of exposure to interferon alfa-2b. Nadofaragene firadenovec (rAd-IFNα/Syn3) consists of rAd-IFNα, a non-replicating recombinant adenovirus vector-based gene therapy that delivers a copy of the human interferon alfa-2b gene to urothelial cells,[9–11] and Syn3, a polyamide surfactant that enhances the viral transduction of the urothelium.[12] Recombinant interferon alfa gene therapy results in local rather than systemic interferon alfa-2b production, and induced tumour regression in preclinical studies.[9–11]

Based on these preclinical results,[9,11,12] a subsequent phase 1 study in patients with BCG-refractory and relapsing non-muscle-invasive bladder cancer confirmed that intravesical nadofaragene firadenovec was well tolerated, with no dose-limiting toxic effects or clinically significant treatment-related adverse events, and a single dose was sufficient to achieve measurable urine interferon alfa.[13,14] In a phase 2 trial of 40 patients with high-grade BCG-refractory and relapsing non-muscle-invasive bladder cancer,[15] 14 patients (35%) were free from high-grade recurrence at 12 months. These encouraging results prompted our study, in which we aimed to evaluate the efficacy and safety of intravesical nadofaragene firadenovec in a larger population of patients with BCG-unresponsive non-muscle-invasive bladder cancer.

Methods

Study design and participants

This phase 3 multicentre, single-arm, open-label, repeat-dose clinical study was done across 33 sites (hospitals and clinics) in the USA. The single-arm study design was based on the 2018 Food and Drug Administration (FDA) guidance that single-arm trials are appropriate for assessment of therapies for patients with BCG-unresponsive non-muscle-invasive bladder cancer because of the paucity of effective available medical therapies, the only alternative being radical cystectomy.[16] Eligible patients were aged 18 years or older at the

time of written informed consent and met the definition of BCG-unresponsive non-muscle-invasive bladder cancer according to the 2018 US FDA Guidance for Industry.[16] This definition encompasses patients with persistent carcinoma in situ, high-grade Ta tumours or high-grade T1 tumours at 6 months despite receiving adequate BCG therapy, which is defined as at least five of the six induction doses and two of the three maintenance treatments of BCG, or at least two of six instillations of a second induction course in which maintenance BCG is not given (previously termed BCG-refractory disease). It also includes patients who have recurrences of high-grade Ta or T1 non-muscle-invasive bladder cancer within 6 months, carcinoma in situ within 12 months of disease-free state after BCG (previously termed BCG relapsed), and patients with persistent high-grade Ta or carcinoma in situ or progression to T1 disease after BCG. Patients were enrolled into two cohorts by diagnosis at enrolment. The carcinoma in situ with or without Ta or T1 cohort included patients with carcinoma in situ with or without concomitant high-grade Ta or T1 non-muscle-invasive bladder cancer (hereafter referred to as the carcinoma in situ cohort). The high-grade Ta or T1 cohort included patients with high-grade Ta or T1 tumours without concomitant carcinoma in situ. Patients had an Eastern Cooperative Oncology Group performance status of 2 or less and a life expectancy of at least 2 years.

Patients were excluded if they had evidence of upper urinary tract disease, urothelial carcinoma within the prostatic urethra, lymphovascular invasion, micropapillary disease, or hydronephrosis due to tumour in the presence of T1 disease. Patients who were on current systemic therapy for bladder cancer or had received pelvic external beam radiotherapy within the previous 5 years were also excluded. Eligible patients had to have a haemoglobin concentration of at least 10 g/dL, white blood cell count of at least 4000 cells per mL, absolute neutrophil count of at least 2000 cells per mL, platelet count of at least 100 000 per mL, aspartate aminotransferase and alanine aminotransferase 1·5 times the upper limit of normal (ULN) or less, total bilirubin 1·5 times the ULN or less, estimated glomerular filtration rate of at least 30 mL/min per 1·73m², and an international normalised ratio and activated partial thromboplastin time less than the institutional ULNs, except in patients receiving anticoagulation therapy, in whom clinically acceptable results were permitted at the investigator's discretion. Patients who received immunosuppressive therapy, investigational drugs (including systemic therapy), or intravesical therapy had to undergo a washout period (3 months before screening for immunosuppressive therapy, 30 days before screening for investigational drugs, and 8 weeks before beginning study treatment for intravesical therapy), with the exception of cytotoxic agents administered as a single instillation immediately after transurethral resection of bladder tumour, which was permitted 14–60 days before beginning the study, and intravesical BCG therapy, which was permitted up to 5 weeks before the diagnostic biopsy required for entry into the study. The full study protocol is included in the appendix.

The protocol and accrual timeline were designed by the Society of Urologic Oncology Clinical Trials Consortium. The study was done in accordance with the Declaration of Helsinki, in compliance with Good Clinical Practice Guidelines. The study protocol was approved by an institutional review board for each centre before accrual. The study procedures and analyses were done per protocol and all protocol amendments were approved by the institutional review board before implementation.

Procedures

At enrolment, all visible tumours were required to be resected, and patients with T1 disease on transurethral resection of bladder tumour had an additional transurethral resection 14–60 days before study treatment. Obvious areas of carcinoma in situ were also fulgurated before beginning study treatment, which was standard practice before BCG administration at all centres.

All patients received 75 mL nadofaragene firadenovec (3×10^{11} viral particles per mL) by intravesical administration through a urinary catheter. Dose reduction was not permitted. The dose and administration regimen was based on results from a previous phase 2 study.[15] After administration, the medication was left in the bladder for 1 h, while patients were asked to rotate positions to maximise bladder surface exposure. Patients received appropriate supportive care as needed, including pre-treatment anticholinergic therapeutic agents on each instillation dosing day to minimise irritative voiding symptoms. Dosing of anticholinergics was not standardised and was at the discretion of the treating physician (or could be omitted if contraindicated).

The screening procedures, including urine cytology and biopsy, were done for all patients up to 28 days before the start of treatment. All patients were evaluated for recurrence with urine cytology and cystoscopy (with biopsy if warranted) at efficacy assessment visits every 3 months. Investigators were not required to use advanced cystoscopic modalities (ie, blue light) for screening and analysis, but, if used, they were advised to use the same modality consistently at screening and at each efficacy assessment for an individual patient. In the absence of high-grade recurrence, administration of nadofaragene firadenovec was repeated at month 3 (day 90), month 6 (day 180), and month 9 (day 270). Patients with recurrence of high-grade disease at months 3, 6, or 9 were removed from the study. Patients who had not withdrawn from treatment had an efficacy assessment at 12 months (365 days) after the first dose of treatment. The cytopathologist was not masked to the study and no centralised pathology review was done for enrolment or cytology assessment. A positive urine cytology and a negative cystoscopy would indicate that further testing or imaging should be done on the entire urinary tract at the discretion of the treating physician. Further details on study schedule procedures (screening, pre-dose, post-dose, and efficacy assessments) are provided in the study protocol (appendix).

Safety assessments (monitoring of adverse events; clinical laboratory evaluations including haematology, urinalysis, and clinical chemistry; vital signs; physical examinations; urinary symptoms; resting 12-lead electrocardiograms; and serum anti-adenoviral antibody concentration) were done on day 1 of each treatment month (every 3 months). Patients were contacted every month between visits by telephone to record adverse events and concomitant medications.

At 12 months after initial treatment, patients had a biopsy of five sites (dome, trigone, right and left lateral wall, and posterior wall) in the bladder. Patients with no evidence of high-grade recurrence could continue receiving nadofaragene firadenovec once every 3 months at the discretion of their treating physician. The study is therefore ongoing, with a 4-year treatment and monitoring phase.

Outcomes

The primary endpoint was the proportion of patients with a complete response in the carcinoma in situ cohort at any time within 12 months after the first dose of nadofaragene firadenovec. Complete response was defined as negative urine cytology and cystoscopy as assessed by the treating physician. If participants had suspicious or malignant cells in urine cytology, with normal cystoscopy and no biopsy done, but had high-grade recurrence at a subsequent visit, the time of recurrence was backdated to the time of the abnormal urine cytology. Secondary endpoints included durability of complete response (defined as the time from first observed complete response to documented tumour recurrence, disease progression, or death) in patients with carcinoma in situ who achieved a complete response, high-grade recurrence-free survival in the Ta or T1 cohort, durability of high-grade recurrence-free survival in both cohorts, radical cystectomy-free survival (defined as the time from the first dose of nadofaragene firadenovec to the first date of cystectomy or death due to any cause) in both cohorts, overall survival in both cohorts, and safety in all treated patients. High-grade recurrence-free survival was defined as surviving patients in whom cystoscopy, cytology, and biopsy examination (if clinically indicated or mandated) showed either no evidence of progression to carcinoma in situ with Ta or T1 lesions, or showed evidence of Ta or T1 lesions without carcinoma in situ that were low grade. A patient was categorised as having high-grade recurrence-free survival at a timepoint if the patient was alive and without documented recurrence of high-grade disease or muscle-invasive disease progression as assessed by the investigator at that timepoint. A patient was judged not to have high-grade recurrence-free survival at the month 3 efficacy assessment visit if urine cytology was reported as suspicious, malignant cells, or not done, and no bladder biopsy was done at the month 3 efficacy assessment visit, and there was high-grade recurrence (confirmed by bladder biopsy) at the next scheduled visit, or biopsy was not done at the next visit but urine cytology result at the next scheduled visit was reported as suspicious or malignant. Overall survival was defined as the time from first dose of nadofaragene firadenovec to death. If death did not occur before end of follow-up then overall survival was censored at the last time the patient was known to be alive before the end of follow-up.

Safety endpoints were type, incidence, relatedness, and severity of adverse events; and number of severe (grade 3 or worse) adverse events as assessed by National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.03).

Additional secondary endpoints were measurement of anti-adenoviral antibody levels at each dosing period, withdrawal, and at 12 months; and durability of response during long-term follow-up. These endpoints are not reported in this paper and will be reported separately.

Statistical analysis

Analyses were done in both the cohort of patients with carcinoma in situ with or without Ta or T1 (the carcinoma in situ cohort) and in the cohort of patients with high-grade Ta or T1 only, but, since the primary endpoint was evaluated in the carcinoma in situ cohort, the sample size calculation was based on that cohort only. The study sample size was based on observations from previous studies, including the phase 2 study in which the observed

complete response rate at any time in patients with carcinoma in situ was 50%. Assuming that this study retained 87·5% of that efficacy, the true response rate would be 43·8%. Enrolling 100 patients with carcinoma in situ would provide 90% power to reject the hypothesis that the true response rate is 27%, at a one-sided alpha of 2·5%. The null hypothesis specified a complete response rate of a true response of 27%, based on observations from previous studies (appendix). An exact p value for the rejection of the null hypothesis was calculated by the Clopper-Pearson method.

The proportion of patients in the carcinoma in situ cohort with a complete response at any timepoint is presented together with a two-sided 95% Clopper-Pearson CI. Efficacy analyses were done per protocol and included patients who met the strict definition of BCG-unresponsive disease. Patients who did not meet the protocol definition of BCG-unresponsive non-muscle-invasive bladder cancer, in accordance with International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use E9 Guidelines,[17] were not included in the efficacy analysis set. Because of the correspondence between hypothesis tests and confidence intervals,[18] the null hypothesis can only be rejected at a one-sided significance level of 2·5% if the two-sided 95% CI lies wholly above 27%.

The proportion of patients in the high-grade Ta or T1 disease cohort who were free from high-grade recurrence at months 3, 6, 9, and 12 is reported together with a two-sided 95% Clopper-Pearson CI. High-grade recurrence-free survival in patients in the high-grade Ta or T1 cohort, in the carcinoma in situ cohort, and in both cohorts combined was evaluated using the Kaplan-Meier method to provide estimates of median duration, along with two-sided 95% CIs for the median and probability of duration every 3 months. The two-sided CI for median duration was computed using the method of Brookmeyer and Crowley. Probability of duration was the Kaplan-Meier estimate of survivor function at each specific timepoint, and the 95% CI for probability of duration was calculated using Greenwood's formula with a log-log transformation. Post-hoc exploratory analyses were done to determine median time to cystectomy among patients in the carcinoma in situ cohort who had complete response, and among patients in the high-grade Ta or T1 cohort who had freedom from high-grade recurrence at month 3.

Continuous data were summarised using descriptive statistics (number of observations, mean, standard deviation, minimum, first quartile, median, third quartile, and maximum), and categorical variables were summarised using frequency counts and percentages. A safety monitoring committee oversaw the study according to the data monitoring plan, and all data analyses were done independently from the principal investigators. Safety analyses were done on the intention-to-treat population.

The significance threshold for p values was 0·05. Statistical analyses were done using SAS version 9.4.

This study is registered with ClinicalTrials.gov, NCT02773849.

Role of the funding source

The funders had no role in study design, data collection, analysis, interpretation, or writing of the report. The primary investigator (SAB) and corresponding author (CPND) had full access to all data in the study and had final responsibility for the decision to submit for publication.

Results

Between Sept 19, 2016, and May 24, 2019, 198 patients were assessed for eligibility. 41 patients were excluded (figure 1). 157 eligible patients were enrolled and received at least one dose of nadofaragene firadenovec. 107 (68%) of 157 patients were diagnosed with carcinoma in situ with or without Ta or T1, and 50 (32%) of 157 patients had high-grade Ta or T1 disease alone. All patients had urothelial cell carcinoma of the bladder and there were no reported histological variants. Median age at baseline was 71 years (IQR 66–77; table 1). The study population was heavily pre-treated, with 78 (50%) of 157 patients having previously received at least three courses of BCG.

Six patients (four in the carcinoma in situ cohort and 2 in the high-grade Ta or T1 cohort) were excluded from the efficacy analysis set because they did not meet the protocol definition of BCG-unresponsive non-muscle-invasive bladder cancer, discovered after these patients had received their first dose of nadofaragene firadenovec. 151 patients were included in the efficacy analysis set (103 in the carcinoma in situ cohort and 48 in the high-grade Ta or T1 cohort). At the time of data analysis cutoff (July 8, 2019) all patients had completed either the month 12 efficacy assessment visit, or had withdrawn from treatment and completed a safety assessment.

55 (53·4%) of 103 patients (95% CI 43·3 to 63·3) in the carcinoma in situ cohort had a complete response, with all complete responses noted at month 3 (table 2). Median follow-up for this cohort was 19·7 months (IQR 16·0–24·8). The pre-specified null hypothesis of a complete response rate no more than 27% is therefore rejected at $p<0·0001$. Median duration of complete response in patients with carcinoma in situ was 9·69 months (95% CI 9·17 to not estimable; figure 2A), with 25 of 103 patients (24·3%; 95% CI 16·4 to 33·7) remaining high-grade recurrence free at 12 months. 25 (45·5%) of the 55 patients with an initial complete response in the carcinoma in situ cohort remained free from high-grade recurrence at 12 months. As described in the methods, if participants had suspicious or malignant urine cytology with a normal cystoscopy, but had high-grade biopsy-proven recurrence at a subsequent visit, the time of recurrence was backdated to the time of the abnormal urine cytology. This applied to seven patients in the cohort. 73 (71%) of 103 patients in the carcinoma in situ cohort developed recurrent high-grade non-muscle-invasive bladder cancer and five (5%) progressed to detrusor muscle invasion (grade pT2 or higher). Three of the five patients who progressed to muscle-invasive bladder cancer had a history of T1 non-muscle-invasive bladder cancer at trial entry, two (2%) had recurrence with carcinoma in situ (one at month 3 and one at month 9; these two patients had occult pT2 tumour identified at radical cystectomy).

In the high-grade Ta or T1 cohort, 35 of 48 patients (72·9%; 95% CI 58·2 to 84·7) were high-grade recurrence-free at month 3, and 21 patients (43·8%; 29·5 to 58·8) were recurrence-free at month 12. Thus, 21 (60%) of 35 patients with high-grade Ta or T1 non-muscle-invasive bladder cancer who were high-grade recurrence-free at 3 months maintained that status at 12 months. Median follow-up for the high-grade Ta or T1 cohort was 20·2 months (IQR 17·2–25·5). Median duration of high-grade recurrence-free survival was 12·35 months (95% CI 6·67 to not estimable; figure 2B).

23 (48%) of 48 patients in this cohort had a biopsy-proven recurrence of high-grade non-muscle-invasive bladder cancer during follow-up, one (2%) died of a non-bladder cancer-related cause (with no evidence of recurrence), and three (6%) progressed to muscle-invasive bladder cancer. Of these three patients, two were identified with occult muscle-invasive bladder cancer at radical cystectomy (one of whom had recurrence at month 9 with carcinoma in situ and was found to have pT2bN0 muscle-invasive bladder cancer at time of cystectomy, and the other was found to have pT2aN0 muscle-invasive bladder cancer after cT1 non-muscle-invasive bladder cancer recurrence at month 12).

Six patients (three in each cohort) with a normal cystoscopy had carcinoma in situ at the time of the protocol-mandated 12-month biopsy. These patients were considered to have had high-grade tumour recurrence, but five of these six patients would actually have been considered free from high-grade recurrence on the basis of cytology and cystoscopy alone (if the biopsies had not been done), and one participant did have a suspicious urine cytology at month 3.

Recurrences of any stage were observed in 104 (69%) of 151 efficacy-evaluable patients in the entire study population, with high-grade non-muscle-invasive bladder cancer observed in 96 (61%) patients (73 in the carcinoma in situ cohort and 23 in the Ta or T1 cohort), progression to muscle-invasive bladder cancer in eight (5%) patients (five in the carcinoma in situ cohort and three in the high-grade Ta or T1 cohort), and on-study non-bladder cancer-related death in one (1%) patient (in the high-grade Ta or T1 cohort). High-grade recurrence-free survival at 1 year in the entire population was 30·5% (95% CI 23·2–38·5; post hoc exploratory analysis).

40 (26%) of 151 patients underwent cystectomy by the month 12 data cutoff, including 30 (29%) of 103 patients in the carcinoma in situ cohort, with a median time to cystectomy of 8·87 months (IQR 4·93–11·01), and ten (21%) of 48 patients in the high-grade Ta or T1 cohort, with median time to cystectomy of 8·31 months (5·78–13·11). In a post-hoc exploratory analysis in the carcinoma in situ cohort, patients who achieved a complete response had a significantly longer median time to cystectomy (11·35 months, IQR 7·67–14·93) compared with those who did not (6·36 months, 4·17–10·64; p=0·043). In a post-hoc exploratory analysis in the high-grade Ta or T1 cohort, patients who were free of high-grade recurrence at month 3 had significantly longer median time to cystectomy (12·42 months, IQR 9·79–14·32) than did those with high-grade recurrence at month 3 (5·31 months, 4·37–6·06; p=0·0095). 24-month cystectomy-free survival in all 151 patients was 64·5% (95% CI 53·6–73·4) and was similar between the cohorts (appendix p 3).

Pathological data were available for all but two patients (one in each cohort). Five (12·5%) of 40 patients were upstaged to muscle-invasive or extravesical disease at cystectomy. Among 30 patients in the carcinoma in situ cohort who underwent cystectomy, one (3·3%) patient was downstaged to pT0 and three (10%) were upstaged to pT2 or greater, including one patient with pT2N1 disease who had recurrence with carcinoma in situ after nadofaragene firadenovec and progressed after subsequent treatment with pembrolizumab. Two of these three patients also had history of cT1 non-muscle-invasive bladder cancer before entering the trial with carcinoma in situ. Of ten patients in the high-grade Ta or T1 cohort who underwent cystectomy, four (40%) had occult carcinoma in situ present in the cystectomy specimen, and two (20%) were identified with occult muscle-invasive bladder cancer.

After six deaths overall (four in the carcinoma in situ cohort and two in the high-grade Ta or T1 cohort), 24-month overall survival was 91·9% (95% CI 80·9–96·7) in all patients who received at least one dose of nadofaragene firadenovec (91·2% [95% CI 74·7–97·1] in the carcinoma in situ cohort, and 93·5% [75·0–98·5] in the high-grade Ta or T1 cohort; appendix p 5).

146 (93%) of 157 patients had adverse events during the study. 110 (70%) patients had events that were study drug-related (table 3). The most frequently reported drug-related adverse events were discharge around the catheter during instillation, fatigue, bladder spasms, and micturition urgency (table 3, appendix p 1). For most patients, the adverse events were transient and were classified as either grade 1 or 2. Grade 3 or 4 adverse events occurred in 29 (18%) of 157 patients, of whom only six (4%) had events that were study drug-related (two cases of micturition urgency, and one case each of bladder spasms, urinary incontinence, syncope, and hypertension). A grade 4 event of sepsis was considered study drug-unrelated but was procedure-related. There were no grade 5 adverse events. 14 (9%) of 157 patients had a total of 26 serious adverse events, of which three (2%) were designated related to drug or procedure (the aforementioned events of syncope and sepsis and one case of haematuria). The remaining serious adverse events were related to patient comorbidities, and there were no frequent serious adverse events (appendix p 2). Three patients discontinued the study drug due to adverse events (one due to bladder spasms, one due to discharge around the catheter during instillation, and one due to the identification of a benign neoplasm of the bladder [urothelial hyperplasia] that was believed by the investigators to be related to the study drug).

Five (3%) of 157 patients died during long-term follow-up when they were off treatment (three secondary to a cardiac event, one pneumonia, and one cause of death unknown). All five deaths occurred at least 4 months after the last administration of the study drug.

Discussion

Intravesical nadofaragene firadenovec was efficacious, with a favourable benefit:risk ratio, in patients with BCG-unresponsive non-muscle-invasive bladder cancer. More than half of patients with BCG-unresponsive carcinoma in situ with or without Ta or T1 had a complete response, with nearly half of those patients were free from high-grade recurrence at 12

months. A similar clinically meaningful response and durability of recurrence-free survival was seen in patients with high-grade Ta or T1 BCG-unresponsive non-muscle-invasive bladder cancer.

The optimal management of patients with BCG-unresponsive non-muscle-invasive bladder cancer represents a challenging clinical dilemma, with few effective therapeutic options available outside of radical cystectomy.[19]

Although potentially curative, radical cystectomy is associated with a complication rate of 30–57% within 90 days after surgery and an inpatient mortality rate of 3–4%.[20,21] Additionally, many patients are either not eligible for surgery due to medical comorbidities or have made an informed decision to decline surgery. For years, the only FDA-approved treatment for these patients has been valrubicin, which was approved more than 20 years ago, and is associated with a complete response rate of just 10% at 12 months.[22] Alternative intravesical therapies that have been investigated include gemcitabine and docetaxel monotherapy,[23,24] combinations including gemcitabine plus mitomycin and gemcitabine plus docetaxel,[25] and nabpaclitaxel.[26] Widespread adoption of these agents has been hampered by small sample sizes, heterogeneous cohorts, and absence of industry-sponsored prospective trials.[27]

The dearth of effective treatment options for BCG-unresponsive non-muscle-invasive bladder cancer led to a collaborative effort beginning in 2012 between the Society of Urologic Oncology, the American Urologic Association, and the FDA, with an initial focus of defining a pathway for drug registration to stimulate drug development in this space.[5,16,28,29] These efforts led to the acceptance of a single-arm trial design for testing novel therapies in patients with BCG-unresponsive non-muscle-invasive bladder cancer. Furthermore, this collaborative group accepted that the primary endpoint for these trials would be the rate and durability of a complete response for carcinoma in situ, with anticipation of an incremental but meaningful improvement in outcome compared with that of valrubicin.

The approval of the intravenous checkpoint inhibitor pembrolizumab every 3 weeks was based on the data from the single-arm KEYNOTE-057 trial in 96 patients with carcinoma in situ with or without high-grade Ta or T1.[6] The reported complete response rate was 41·0% (95% CI 31·0–51·0), with a median response duration of 16·2 months (range 0·0 to longer than 30·4 months).[6]

Progression to muscle invasion was a rare event in our trial, occurring in 5% of patients in the carcinoma in situ cohort and 6% of patients in the high-grade Ta or T1 cohort. These rates of progression are lower than those previously reported[30] for patients with BCG-unresponsive non-muscle-invasive bladder cancer treated with immediate cystectomy, suggesting that nadofaragene firadenovec did not put patients at increased risk for progression and subsequent death from bladder cancer, and might have prevented disease progression.[30] Moreover, cystectomy-free survival at 24 months for the total study population was 64·5%, indicating that most patients with this difficult-to-treat condition chose to avoid surgery.

Three patients who underwent cystectomy in the carcinoma in situ cohort had pT2 or higher stage disease. Two of the three patients had a remote history of cT1 disease before entering the trial, suggesting that these patients might have been understaged at screening. The presence of concomitant carcinoma in situ on final pathology on four patients in the high-grade Ta or T1 cohort highlights the prevalence of carcinoma in situ at the time of cystectomy and is in line with previous reports.[31] It is likely that many patients with high-grade Ta or T1 tumours also had occult carcinoma in situ at initial diagnosis, which was undetected until cystectomy.

The dosing schedule of nadofaragene firadenovec (one intravesical treatment every 3 months) was convenient for both patients and physicians. The safety profile of nadofaragene firadenovec was acceptable, with only three patients stopping treatment due to an adverse event, no treatment-related deaths, and no pattern of immune-related adverse events noted.

Several additional agents are under investigation for the treatment of this disease.[27] Issues of benefit, risk, cost, and delivery will need to be considered as new agents emerge for patients with BCG-unresponsive non-muscle-invasive bladder cancer. A strength of this study was its protocol-mandated bladder biopsies at 12 months, to substantiate the complete responses observed before commencing longer-term follow-up and durability assessments of nadofaragene firadenovec. The 12-month mandated biopsy also provides a confirmation of the observed recurrence-free survival and an opportunity to switch patients to alternative treatments for recurrent disease.

Limitations of the study include the absence of central pathology review and the fact that initial responses were based on cystoscopy and cytology results, which can be subjective. Although the experience and diagnostic criteria being used by a pathologist can influence outcomes, our approach of interpreting data from cytology and cystoscopies (with biopsies when appropriate) at regular interval aligns with standard clinical practice, and strengthens the real-world generalisability of the findings. Another limitation is that advanced cystoscopy techniques, such as blue-light imaging, were not mandated and their use was left up to the discretion of the treating physician. At the time of study design, we did not consider it appropriate or feasible to mandate advanced cystoscopy, given that not all sites have access to the technology, and hexaminolevulinate was not approved by the FDA for use with flexible cystoscopy in the USA at the time. To minimise potential heterogeneity, investigators were advised to use the same imaging modality at screening and efficacy assessments for an individual patient. Additionally, the quality of a transurethral resection of bladder tumour is an important factor in determining the risks of recurrence and progression in patients with non-muscle-invasive bladder cancer, and although the resection technique was not standardised in this study, the results reflect the potential efficacy outcomes of nadofaragene firadenovec in a real-world setting across a range of centres with experienced urologists. Finally, blood and urine samples collected from patients per protocol will be analysed for biomarkers at a later date. These analyses could help to identify early treatment responders and provide insight into the potential mechanisms of treatment non-response.

In summary, intravesical nadofaragene firadenovec for patients with BCG-unresponsive non-muscle-invasive bladder cancer showed, to our knowledge, first-of-its-kind efficacy for gene

therapy, with a manageable safety profile and delivery schedule, resulting in a favourable benefit:risk profile. These data support nadofaragene firadenovec as a potentially important therapeutic advancement for a historically difficult-to-treat disease.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Research in context

Evidence before this study

The standard of care for high-risk (carcinoma in situ, high-grade Ta or T1 tumours) non-muscle-invasive bladder cancer after transurethral resection of the bladder tumour is intravesical BCG. However, most patients with high-risk non-muscle-invasive bladder cancer eventually become unresponsive to BCG and have recurrence within 1 year. The only US Food and Drug Administration (FDA)-approved bladder-sparing treatment option is the intravesical chemotherapy agent valrubicin, which shows poor efficacy. We searched PubMed using the search term “non-muscle-invasive bladder cancer” for clinical studies and congress abstracts, with no language restrictions, from Sept 1, 2015, to May 19, 2020. The immune modulator pembrolizumab was approved in patients with BCG-unresponsive, high-risk non-muscle-invasive bladder cancer with carcinoma in situ on the basis of results from a phase 2, single-arm study. Despite reported efficacy, pembrolizumab is associated with systemic immune-related side-effects, and the indication does not include patients with high-grade Ta or T1 tumours. We aimed to evaluate intravesical delivery of recombinant interferon alfa-2b gene in patients with high-grade non-muscle-invasive bladder cancer who have BCG failure. We adopted a single-arm design (per FDA guidelines) as there is no standard treatment for this patient population.

Added value of this study

Intravesical delivery of the adenoviral vector containing the human recombinant interferon alfa-2b gene exposes the bladder to a greater extent than instilling the cytokine protein itself, which is only retained for an hour or two. Ours is a novel approach that is, to our knowledge, not otherwise reported in the literature for this indication, aside from earlier phase trials of this same agent. In this phase 3 study, nadofaragene firadenovec showed clinical efficacy and safety in patients with BCG-unresponsive non-muscle-invasive bladder cancer with carcinoma in situ and high-grade Ta or T1 tumours. More than half of patients with carcinoma in situ (with or without a high-grade Ta or T1 tumour) showed a complete response, and median response duration and high-grade recurrence-free survival were promising during long-term treatment.

Implications of all the available evidence

Intravesical nadofaragene firadenovec offers an additional therapeutic option in this difficult-to-treat population. Intravesical nadofaragene firadenovec is associated with an acceptable safety profile and promising efficacy outcomes to offer a realistic alternative to chemotherapy and systemic treatment options. These results were consistent with findings from the phase 2 study, which suggest that nadofaragene firadenovec is an efficacious and well tolerated intravesical bladder-sparing therapy. Moreover, intravesical nadofaragene firadenovec treatment has a favourable dosing schedule (one intravesical treatment once every 3 months) that can be managed easily by both patient and clinician. Future research should include analyses to help to identify early treatment responders and provide insights into the potential mechanisms of treatment non-response.

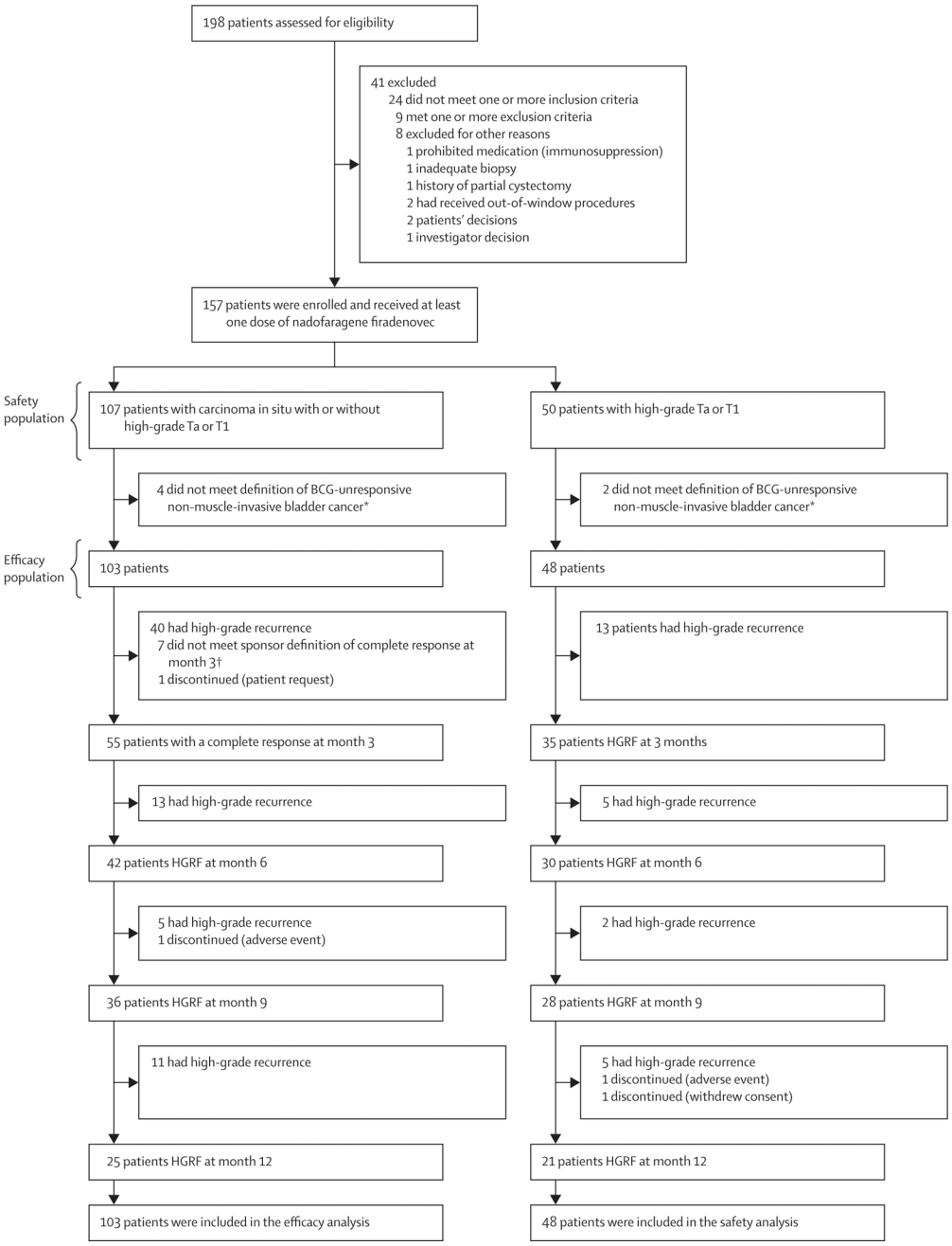

Figure 1: Trial profile

HGRF=high-grade recurrence-free. *Post-enrolment review of medical records. †Defined in the final Statistical Analysis Plan. Five patients in the carcinoma in situ Ta or T1 cohort and three patients in the high-grade Ta or T1 cohort progressed to detrusor muscle invasion (≥pT2) by data cutoff.

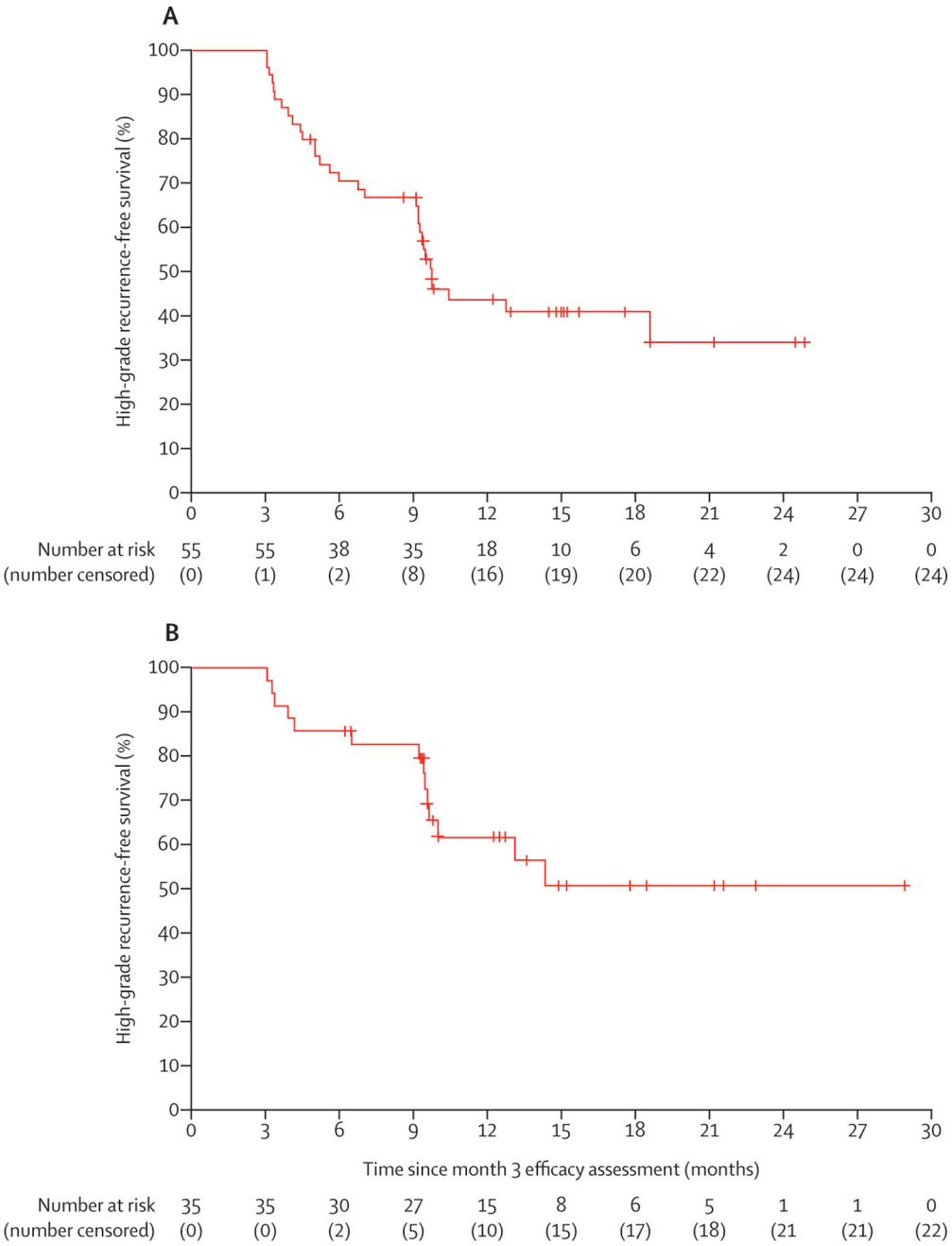

Figure 2: High-grade recurrence-free survival in patients with non-muscle-invasive bladder cancer given nadofaragene firadenovec, in patients who had a complete response at 3 months

(A) Patients with carcinoma in situ, with or without Ta or T1. (B) Patients with high-grade Ta or T1.

Table 1:

Patient characteristics at baseline

	Carcinoma in situ cohort (n=107)	High-grade Ta or T1 cohort (n=50)	All enrolled patients (n=157)
Age at baseline, years	72 (66–77)	71 (64–78)	71 (66–77)
Sex			
Male	95 (89%)	34 (68%)	129 (82%)
Female	12 (11%)	16 (32%)	28 (18%)
Race			
White	99 (93%)	47 (94%)	146 (93%)
Black or African-American	6 (6%)	2 (4%)	8 (5%)
Asian	2 (2%)	1 (2%)	3 (2%)
Time from initial diagnosis of bladder cancer, months	20 (13–35)	15 (12–22)	18 (13–29)
Number of previous courses of BCG administered *			
1	1 (1%)	5 (10%)	6 (4%)
2	45 (42%)	28 (56%)	73 (47%)
3	28 (26%)	12 (24%)	40 (26%)
4	12 (11%)	2 (4%)	14 (9%)
≥5	21 (20%)	3 (6%)	24 (15%)
Stage at baseline			
Carcinoma in situ only	81 (76%)	0	81 (52%)
Ta	0	35 (70%)	35 (22%)
Ta + carcinoma in situ	21 (20%)	0	21 (13%)
T1	0	15 (30%)	15 (10%)
T1 + carcinoma in situ	5 (5%)	0	5 (3%)
ECOG status			
0	97 (91%)	43 (86%)	140 (89%)
1	7 (7%)	6 (12%)	13 (8%)
2	3 (3%)	1 (2%)	4 (3%)

Data are median (IQR) or n (%). CIS=carcinoma in situ. ECOG=Eastern Cooperative Oncology Group.

* A course of BCG was defined as at least five of six initial induction BCG doses plus at least two of three maintenance BCG doses, or at least two of six instillations of a second induction course in which maintenance BCG is not given.

Table 2:

Complete response and freedom from high-grade recurrence in the efficacy population

	Carcinoma in situ cohort (n=103)	High-grade Ta or T1 cohort (n=48)	All patients (n=151)
Patients with complete response at month 3 *	55 (53·4%; 43·3–63·3)	35 (72·9%; 58·2–84·7)	90 (59·6%; 51·3–67·5)
Duration of complete response † or high-grade recurrence-free survival ‡, months	9·69 (9·17-NE)	12·35 (6·67-NE)	7·31 (5·68–11·93)
Patients who were free from high-grade recurrence			
Month 6	42 (40·8%; 31·2–50·9)	30 (62·5%; 47·4–76·0)	72 (47·7%; 39·5–56·0)
Month 9	36 (35·0%; 25·8–45·0)	28 (58·3%; 43·2–72·4)	64 (42·4%; 34·4–50·7)
Month 12	25 (24·3%; 16·4–33·7)	21 (43·8%; 29·5–58·8)	46 (30·5%; 23·2–38·5)

Data are n (%; 95% CI) or median (95% CI). NE=not estimable.

* Patients with a complete response included all patients who had both a complete response reported by the study investigator.

† Patients in the carcinoma in situ cohort.

‡ Patients in the high-grade Ta or T1 cohort.

Table 3:

Study drug-related adverse events

	Grade 1–2	Grade 3	Grade 4–5
Patients with study drug-related adverse events *	103 (66%)	6 (4%)	0
Types of events			
Discharge around the catheter during instillation	39 (25%)	0	0
Fatigue	31 (20%)	0	0
Bladder spasm	24 (15%)	1 (1%)	0
Micturition urgency	22 (14%)	2 (1%)	0
Chills	18 (12%)	0	0
Dysuria	17 (11%)	0	0
Pyrexia	16 (10%)	0	0
Syncope	0	1 (1%)	0
Hypertension	2 (1%)	1 (1%)	0
Urinary incontinence	4 (3%)	1 (1%)	0

Data are n (%). The table shows study drug-related adverse events occurring in at least 10% of all treated patients (n=157) during the study.

* Only one (1%) patient had a grade 1 study drug-related adverse event, which was classified as unknown. Adverse events include all events that occurred or worsened after the first dose of nadofaragene firadenovec. There were no grade 4 or 5 study drug-related adverse events.