Low Rate of Cystectomy and Delayed Median Time to Cystectomy Among Patients Who Achieved Complete Response With Nadofaragene Firadenovec

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ABSTRACT

Introduction

Patients with bacillus Calmette-Guérin (BCG)-unresponsive high-grade non-muscle invasive bladder cancer (NMIBC) are at significant risk for disease progression. While cystectomy can be curative in this setting, it is associated with high perioperative morbidity, a risk of mortality, and decreased quality of life. Thus, most patients with BCG-unresponsive NMIBC either decline or are deemed ineligible for cystectomy. There is an unmet medical need for effective bladder-preserving treatment options. Nadofaragene firadenovec is a non-replicating recombinant adenovirus vector-based gene therapy. This phase 3 study assessed its safety and efficacy in 157 patients with HG BCG-unresponsive NMIBC. The study met its primary endpoint with 53.4% of patients with CIS±Ta/T1 achieving a complete response (CR), all by 3 months. 43.6% of these patients remained free of HG recurrence at 15 months. Herein we report the incidence of and time to cystectomy, a key secondary objective of the phase 3 study.

Methods

The multicenter, open-label phase 3 study enrolled patients into two cohorts: CIS±Ta/T1 (carcinoma in situ with or without high-grade Ta or T1) and HG Ta/T1 (HG Ta or T1 without concomitant CIS) with 103 and 48 patients, respectively, included in the efficacy analysis. Nadofaragene (3×10 vp/mL [75 mL]) was administered once every 3 months for up 4 doses, with additional dosing at the investigator's discretion. The protocol mandated a 5-site (dome, trigone, right and left lateral walls, posterior wall) biopsy at 12 months. This analysis was based on the data cut-off at 12 months.

Results

A total of 40 (26.5%) patients underwent cystectomy, including 30 (29.1%) in the CIS±Ta/T1 cohort with median time to cystectomy being 8.87 months, and 10 (20.8%) in the HG Ta/T1 cohort with median time to cystectomy being 8.31 months. Within the CIS±Ta/T1 cohort, patients who achieved CR had significantly longer median time to cystectomy compared to those who did not (p=0.0432; 11.35 vs 6.36 months, respectively). Within the HG Ta/T1 cohort, patients who were free of HG recurrence at month 3 also had significantly longer median time to cystectomy versus those with HG recurrence at 3 months (p=0.0095; 12.42 vs 5.31 months, respectively). The cystectomy-free survival among all treated patients was 64.5% at 24 months and was similar between the cohorts.

Conclusion

Of patients with HG BCG-unresponsive NMIBC treated with nadofaragene firadenovec, 73.5% remained free of cystectomy at 12 months. The rate of cystectomy is lower with nadofaragene firadenovec compared to historical data of 30%-50% with other salvage intravesical therapies. Nadofaragene firadenovec is an effective bladder-sparing treatment for patients with HG BCG-unresponsive NMIBC as demonstrated by lower rate of cystectomy and longer median time to cystectomy. Clinical trial information: NCT02773849

BACKGROUND

- Patients with bacillus Calmette-Guérin (BCG)-unresponsive high-grade (HG) non-muscle invasive bladder cancer (NMIBC) are at significant risk for disease progression
- Radical cystectomy currently offers the most definitive cancer treatment in this setting; however, it is associated with high perioperative morbidity and many patients are unwilling or ineligible to undergo the procedure
- There is an unmet medical need for effective bladder-preserving intravesical treatment options
- Nadofaragene firadenovec is a non-replicating recombinant adenovirus vector-based gene therapy
- Nadofaragene firadenovec is a replication-deficient recombinant type 5 adenovirus vector-based gene therapy that delivers a copy of the human interferon alpha-2b (IFNα2b) gene into the bladder epithelium
- The phase 3 study assessed its safety and efficacy in 157 patients with HG BCG-unresponsive NMIBC (NCT02773849)
  - The study met its primary endpoint
  - 53.4% of patients with CIS±Ta/T1 achieved a complete response (CR), all by 3 months
  - 43.6% of these patients remained free of high-grade recurrence at 15 months
- Herein we report the incidence of and time to cystectomy, a key secondary objective of the phase 3 study

METHODS

- The multicenter, open-label phase 3 study enrolled patients into 2 cohorts: CIS±Ta/T1 and high-grade Ta/T1 with 103 and 48 patients, respectively, included in the efficacy analysis
- Nadofaragene (3×10 vp/mL [75 mL]) was administered once every 3 months for up 4 doses, with additional dosing at the investigator's discretion. The protocol mandated a 5-site (dome, trigone, right and left lateral walls, posterior wall) biopsy at 12 months

Patient Population

High-grade BCG-unresponsive NMIBC[a] N=157

Key Inclusion Criteria

- High-grade BCG-unresponsive NMIBC patients
- ≥18 years and ECOG PS ≤2
  1. CIS±Ta/T1 (CIS with or without high-grade Ta/T1)
  2. High-grade Ta/T1 (without concomitant CIS)

Key Exclusion Criteria

- Current or previous evidence of muscle invasive (muscularis propria) or metastatic disease
- Intravesical therapy within 8 weeks prior to beginning study treatment

[a]BCG-unresponsive NMIBC is defined as: (1) persistent high-grade recurrence ≤12 months after BCG initiation; (2) relapse with CIS after initial complete response ≤12 months after last BCG treatment; or (3) relapse with high-grade Ta/T1 NMIBC ≤6 months after last BCG treatment.

- Radical cystectomy-free survival was a secondary endpoint of the study
- These analyses were based on the data cut-off at 15 months

RESULTS

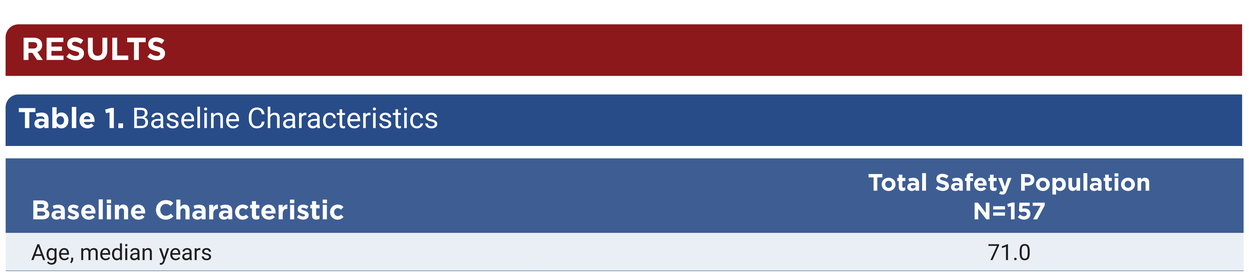
Table 1. Baseline Characteristics

Baseline Characteristic		Total Safety Population N=157
Age, median years		71.0
Male, n%		129 (82)
Time from initial diagnosis of bladder cancer, median months		18
ECOG Performance Status 0, n (%)		140 (89)
Prior radiotherapy, n (%)		5 (3)
BCG failure classification, n (%)	Relapsed Refractory	64 (41) 93 (59)
Number of prior BCG courses[a], n (%)	1 2 ≥3	6[a] (4) 73 (46) 78 (50)
Stage at entry, n (%)	CIS only Ta Ta + CIS T1 T1 + CIS	81 (52) 35 (22) 21 (13) 15 (10) 5 (3)

[a]1 patient in the CIS±Ta/T1 and 5 patients in the high-grade Ta/T1 cohort who were BCG refractory at enrollment.

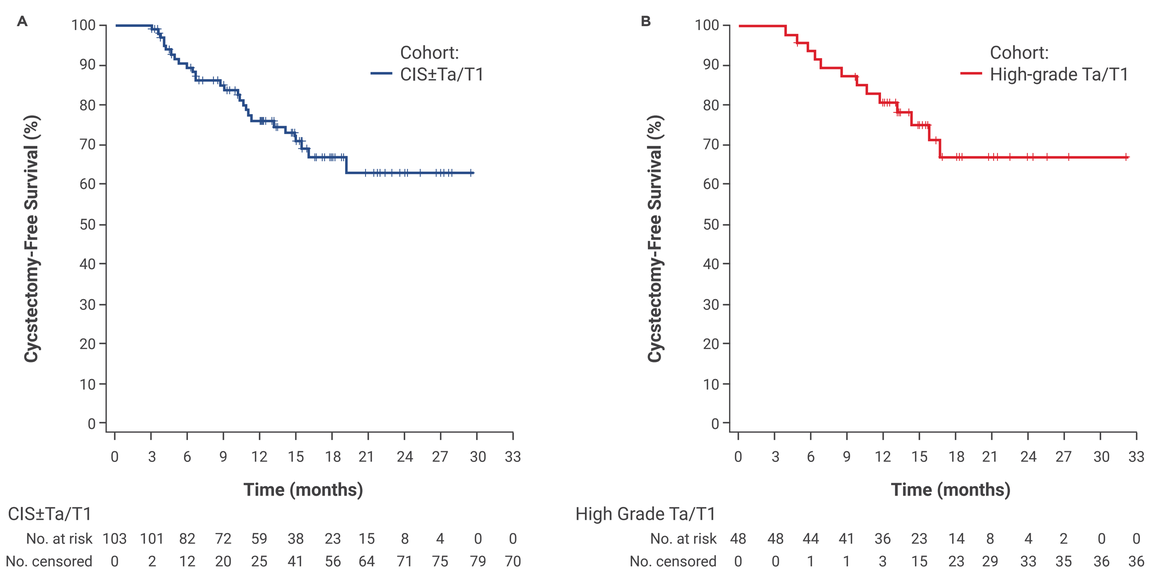
- At baseline, patients had median age of 70.8 years; 82.2% were male. The median prior lines of therapy, non-BCG regimen, and courses of BCG, were 3, 0, and 2, respectively.

Figure 1. Median Time to Cystectomy



- 74% of patients were free of cystectomy by 12 months
- A total of 40 (26.5%) patients underwent cystectomy
  - CIS±Ta/T1 cohort: 30/103 (29.1%) with median of 8.87 months to cystectomy
  - High-grade Ta/T1 cohort: 10/48 (20.8%) with median of 8.31 months to cystectomy
- Among patients with cystectomy
  - Within the CIS±Ta/T1 cohort, the time to cystectomy was significantly longer for patients who achieved CR versus patients who did not (P=0.04)
  - Within the high-grade Ta/T1 cohort, the time to cystectomy is significantly longer among patients who were free of high-grade recurrence at 3 months versus patients who had high-grade recurrence (P=0.01)

Figure 2. Cystectomy-Free Survival[a]



[a]Cystectomy-free survival was defined as the time from the first dose to the first date of cystectomy or death due to any cause. Patients who were alive with no cystectomy performed were censored at their last contact date with known status for cystectomy. Cystectomy-free survival rate is Kaplan-Meier estimate of survivor function at each specific time point. The 95% CI is calculated using Greenwood's formula with a log-log transformation.

- 24-month cystectomy-free survival was 64.5% among all treated patients and was similar between cohorts

Table 2. Adverse Events

	Total Safety Population N=157 n (%)
Adverse events	
Any AEs	146 (93)
Serious AEs	17 (11)
CTCAE Grade 3 AEs	29 (19)
Grade 4 AEs	2[a] (1)
Grade 5 AEs	0 (0)
Study-related adverse events	
Any drug-related AEs (local and systemic)	110 (70)
Any procedure-related AEs	76 (48)
Serious drug- or procedure-related AEs	4[b] (3)
CTCAE Grade 3 AEs	6[c] (4)
Grade 4 AEs	0 (0)
Discontinuation of study drug due to	
Any AEs	4[d] (3)
Study drug- or procedure-related AEs	4[d] (3)

[a]1 sepsis, 1 anaphylactic reaction.
[b]1 grade 4 sepsis, 1 grade 3 syncope, 1 grade 3 hematuria, and 1 grade 2 pyrexia; these were study drug- or procedure-related serious AEs, and none led to study drug discontinuation.
[c]1 bladder spasm, 2 micturition urgency, 1 urinary incontinence, 1 syncope, and 1 hypertension.
[d]1 grade 3 bladder spasm, 1 grade 2 instillation site discharge, 1 grade 2 benign neoplasm of bladder (urethral hyperplasia, not disease progression), and 1 grade 1 chills.

- The most common AEs (incidence ≥10%): fatigue, instillation site discharge, dysuria, bladder spasm, and urinary tract infection
- With the exception of fatigue and frequency of micturition (median duration of 11 and 41 days, respectively), all frequently occurring, study drug-related AEs were transient, with a median duration of 1-2 days
- Four (3%) patients discontinued study drug due to a study drug-related AE: 3 in the CIS±Ta/T1 cohort (3%) and one in the high-grade Ta/T1 cohort (2%)

Table 3. Most Common (≥10%) Adverse Events

System Organ Class/Preferred Term	N=157 n (%) All Grades	N=157 n (%) Grades 3-4
Instillation site discharge	52 (33)	0 (0.0)
Fatigue	37 (24)	0 (0.0)
Bladder spasm	31 (20)	1[a] (0.6)
Micturition urgency	29 (19)	2[b] (1.3)
Hematuria	26 (17)	0 (0.0)
Pyrexia	25 (16)	0 (0.0)
Dysuria	23 (15)	0 (0.0)
Chills	24 (15)	0 (0.0)
Headache	24 (15)	0 (0.0)
Urinary tract infection	19 (12)	0 (0.0)
Diarrhea	17 (11)	0 (0.0)

[a]1 grade 3 bladder spasm
[b]2 grade 3 micturition urgency

CONCLUSIONS

- These results demonstrate the efficacy of nadofaragene firadenovec regardless of patient characteristics or prior treatment history
- Nadofaragene firadenovec represents a potential novel treatment option for patients with high-grade BCG-unresponsive NMIBC that advances the current treatment paradigm

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Abbreviations

AE, adverse event; BCG, bacillus Calmette Guérin; CIS, carcinoma in situ; CR, complete response; CTCAE, Common Terminology Criteria for Adverse Events; ECOG PS, Eastern Cooperative Oncology Group Performance Status; IFN, interferon; NMIBC, non-muscle invasive bladder cancer; T, tumor.

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