Subgroup Analyses of the Phase 3 Study of Intravesical Nadofaragene Firadenovec in Patients With High-grade, BCG-unresponsive Nonmuscle Invasive Bladder Cancer (NMIBC)

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ABSTRACT

Introduction

The goals of treatment for NMIBC are to reduce recurrence and prevent progression. However, despite optimal treatment, more than 50% of the patients who demonstrated an initial response to BCG will experience recurrence and progression and become BCG-unresponsive. With limited treatment options, there is an unmet medical need for local, effective, bladder-preserving treatment options. Nadofaragene firadenovec is a non-replicating recombinant type 5 adenovirus vector-based gene therapy that delivers a copy of the human IFNα2b gene. The phase 3 study assessed its safety and efficacy in 157 patients with high-grade, 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 high-grade recurrence at 15 months. Subgroup and multivariate analyses were conducted to assess the baseline patient characteristics and clinical factors that may contribute to response and durability of response.

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 high-grade Ta/T1 (high-grade 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. The subgroup analyses were based on the efficacy population for the following subgroups: age group (<70 or ≥70 years); sex; disease status at baseline (BCG-refractory or BCG-relapsed); prior lines of therapy (0 or ≥1); prior non-BCG regimens (≤3 or >3); prior courses of BCG (≤3 or >3). A multivariate analysis was also conducted for confirmation. These analyses were based on the data cut-off at 15 months.

Results

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. For both cohorts, there were no significant differences in response rates at 3 and 15 months between males and females, age groups, BCG-refractory vs BCG-relapsed, ≤3 or >3 prior lines of therapy, 0 or ≥1 prior non-BCG regimens, and ≤3 or >3 prior courses of BCG. There were also no significant differences between the subgroups in duration of response, except in the CIS±Ta/T1 cohort, where patients who had received ≤3 prior courses of BCG had significantly longer duration of response compared to patients who received >3 courses (12.68 vs 4.96 months; *p*=0.0172). Results from multivariable analysis confirmed that none of these baseline characteristics or prior therapy significantly contributed to response rates at 3 and 15 months or duration of response.

Conclusion

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. Clinical trial information: NCT02773849

BACKGROUND

- Disease recurrence is common in high-risk non-muscle invasive bladder cancer (NMIBC) following intravesical therapy
- Within 1 year of intravesical therapy, up to 50% of high-risk patients will experience disease recurrence
- Despite optimal treatment, more than 50% of the patients who demonstrated an initial response to bacillus Calmette-Guérin (BCG) will experience recurrence and progression and become BCG-unresponsive
- For patients with high-risk BCG-unresponsive NMIBC, radical cystectomy is the only treatment option recommended by the American Urological Association (AUA)
- The goals of treatment for NMIBC are to reduce recurrence and prevent progression
- With limited treatment options, there is an unmet medical need for local, effective, bladder-preserving treatment options
- Nadofaragene firadenovec is a replication-deficient recombinant type 5 adenovirus vector-based gene therapy that delivers a copy of the human IFNα2b gene into the bladder epithelium
- The phase 3 study assessed its safety and efficacy in 157 patients with high-grade, BCG-unresponsive NMIBC (NCT02773849)
  - The study met its primary endpoint
  - 53.4% of patients with CIS±Ta/T1 (carcinoma *in situ* with or without high-grade Ta or T1) achieving a complete response, all by 3 months
  - 43.6% of these patients remained free of high-grade recurrence at 15 months
- Subgroup and multivariate analyses were conducted to assess the baseline patient characteristics and clinical factors that may contribute to response and durability of response

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.

- The subgroup analyses were based on the efficacy population for the following subgroups: age group (<70 or ≥70 years); sex; disease status at baseline (BCG-refractory or BCG-relapsed); prior lines of therapy (0 or ≥1); prior non-BCG regimens (≤3 or >3); prior courses of BCG (≤3 or >3)
- A multivariate analysis was also conducted for confirmation
- 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.

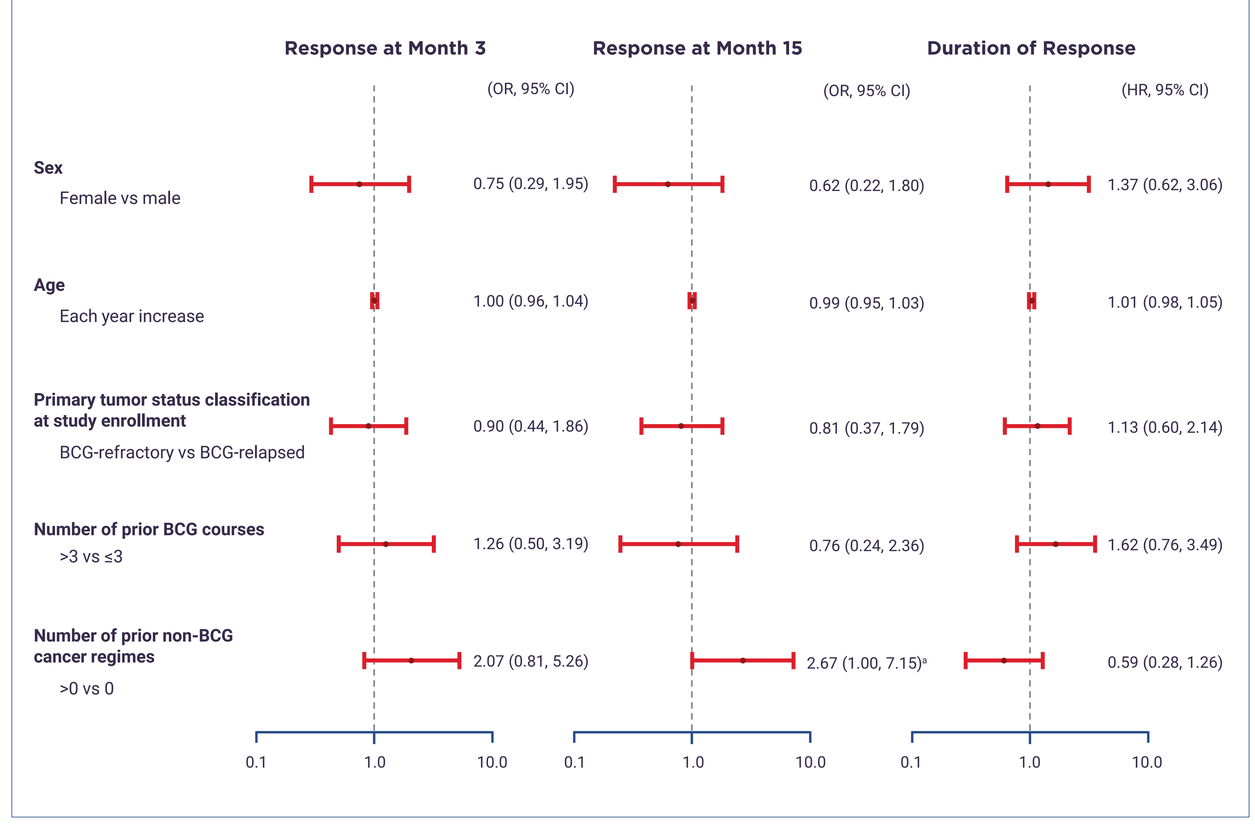
Table 2. Subgroup Analyses

		Responders at 3 Months			Responders at 15 Months					
		Number of Responders	CIS±Ta/T1 n=55	High-grade Ta/T1 n=35	Total Efficacy Population N=90	CIS±Ta/T1 n=24		High-grade Ta/T1 n=19		Total Efficacy Population N=43	
		Percent of Responders in Each Subgroup	CR n (%)	HGRF n (%)	CR + HGRF n (%)	CR n (%)	Duration of CR in Responders, Median Months	HGRF n (%)	Duration of HGRFS in Responders, Median Months	CR + HGRF n (%)	Duration of CR or HGRFS in Responders, Median Months
Sex	Male	48 (87)	26 (74)	74 (82)	22 (92)	10.41	14 (74)	17.05	36 (84)	14.32
	Female	7 (13)	9 (26)	16 (18)	2 (8)	9.17	5 (26)	NR	7 (16)	11.38
	P-value	0.7674	0.4805	1.0000	0.7276	0.1755	1.0000	0.9085	1.0000	0.6609
Age	<70 years	26 (47)	17 (49)	43 (48)	13 (54)	NR	9 (47)	NR	22 (51)	NR
	≥70 years	29 (53)	18 (51)	47 (52)	11 (46)	9.43	10 (53)	14.32	21 (49)	9.99
	P-value	0.5506	0.7456	0.3218	0.2509	0.3071	1.0000	0.4650	0.3644	0.2007
Disease Classification at Baseline	BCG-refractory	28 (51)	24 (69)	52 (58)	12 (50)	10.07	12 (63)	14.32	24 (56)	12.68
	BCG-relapsed	27 (49)	11 (31)	38 (42)	12 (50)	9.69	7 (37)	NR	19 (44)	NR
	P-value	0.6928	0.7279	0.7393	0.8162	0.9010	0.5171	0.2817	0.7145	0.5774
Number of Prior Total Lines of Therapy	≤3	31 (56)	26 (74)	57 (63)	14 (58)	10.41	15 (79)	17.05	29 (67)	14.32
	>3	24 (44)	9 (26)	33 (37)	10 (42)	9.69	4 (21)	NR	14 (33)	9.69
	P-value	1.0000	0.2479	0.8631	1.0000	0.5625	1.0000	0.5638	0.7077	0.3233
Number of Prior Courses of BCG at Baseline	≤3	40 (73)	30 (86)	70 (78)	20 (83)	12.68	17 (89)	17.05	37 (86)	17.05
	>3	15 (27)	5 (14)	20 (22)	4 (17)	4.96	2 (11)	9.40	6 (14)	4.96
	P-value	0.4004	0.3043	0.4464	0.1293	**0.0172**[a]	1.0000	0.2635	0.0622	**0.0056**[a]
Number of Prior Non-BCG Regimens	0	36 (65)	29 (83)	65 (72)	13 (54)	18.56	16 (84)	NR	29 (67)	18.56
	≥1	19 (35)	6 (17)	25 (28)	11 (46)	9.43	3 (16)	17.05	14 (33)	12.68
	P-value	0.3895	0.6561	0.4461	0.0751	0.3141	1.0000	0.7692	0.2146	0.4240

[a]Significant

- For both cohorts, there were no significant differences in response rates at 3 and 15 months between males and females, age groups, BCG-refractory versus BCG-relapsed, ≤3 or >3 prior lines of therapy, 0 or ≥1 prior non-BCG regimens, and ≤3 or >3 prior courses of BCG
- There were also no significant differences between the subgroups in duration of response, except in the CIS±Ta/T1 cohort, where patients who had received ≤3 prior courses of BCG had significantly longer duration of response compared to patients who received >3 courses (12.68 vs 4.96 months; *P*=0.0172)

Figure 1. Multivariable Analyses



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; AUA, American Urological Association; BCG, bacillus Calmette Guérin; CIS, carcinoma in situ; CR, complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; HGRF, high-grade recurrence free; HGRFS, high-grade recurrence-free survival; IFN, interferon; NMIBC, non-muscle invasive bladder cancer; NR, not reached; PS, performance status.

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