# 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 (rAd-IFNa/Syn3) 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) with the study meeting 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<br>Refractory | 64 (41)<br>93 (59) |
| Number of prior BCG courses[a], n (%) | 1<br>2<br>≥3 | 6[a] (4)<br>73 (46)<br>78 (50) |
| Stage at entry, n (%) | CIS only<br>Ta<br>Ta + CIS<br>T1<br>T1 + CIS | 81 (52)<br>35 (22)<br>21 (13)<br>15 (10)<br>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.

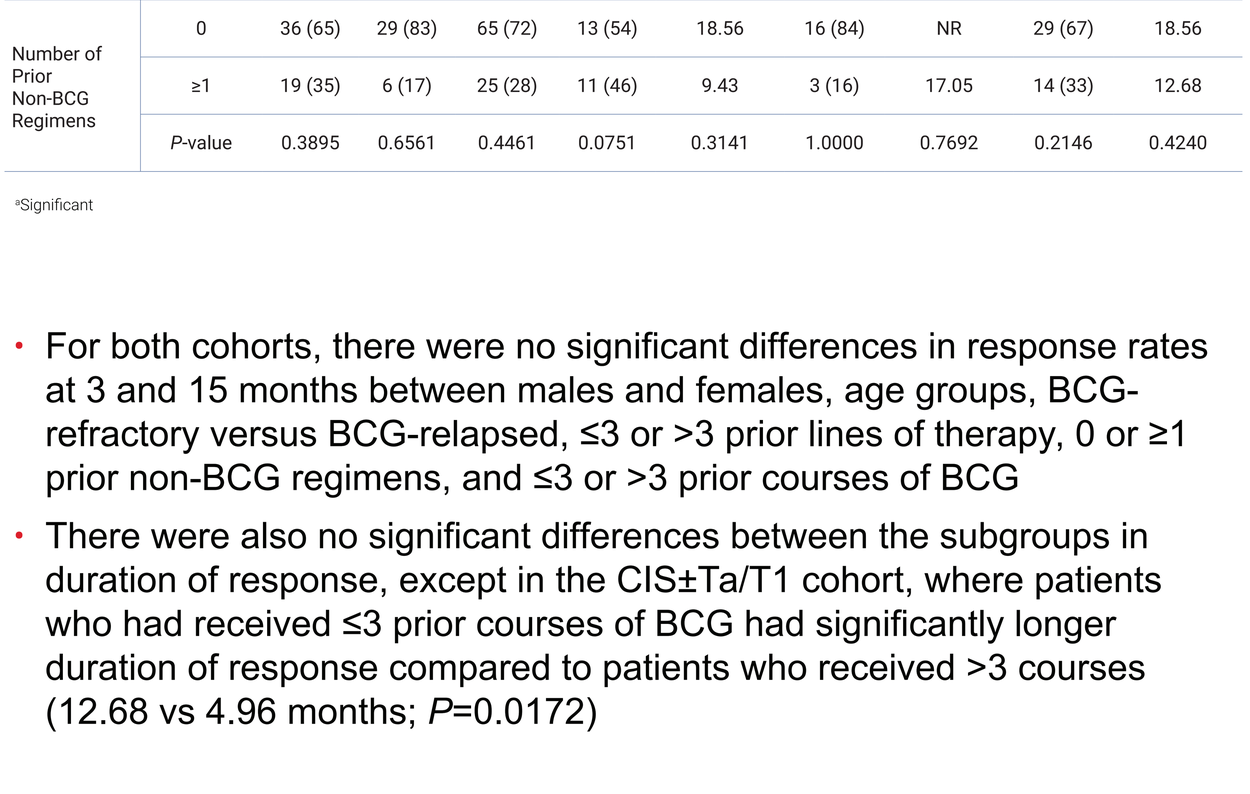
**Table 2.** Subgroup Analyses

| | | 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

### 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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### Funding

Study supported by FKD Therapies Oy, Finland; graphics provided by Truposha, LLC, supported by FerGene, Inc.

*Presented at the 21st Annual Meeting of the Society of Urologic Oncology (SUO); Virtual Meeting; December 3-5, 2020.*