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Brief Correspondence

Antiadenovirus Antibodies Predict Response Durability to Nadofaragene Firadenovec Therapy in BCG-unresponsive Non–muscle-invasive Bladder Cancer: Secondary Analysis of a Phase 3 Clinical Trial

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Abstract

A recent phase 3 trial of intravesical nadofaragene firadenovec reported a promising complete response rate for patients with bacillus Calmette-Guérin–unresponsive non–muscle-invasive bladder cancer. This study examined the ability of antiadenovirus antibody levels to predict the durability of therapeutic response to nadofaragene firadenovec. A standardized and validated quantitative assay was used to prospectively assess baseline and post-treatment serum antibody levels among 91 patients from the phase 3 trial, of whom 47 (52%) were high-grade recurrence free at 12 mo (responders). While baseline titers did not predict treatment response, 3-mo titer >800 was associated with a higher likelihood of durable response ($p = 0.026$). Peak post-treatment titers >800 were noted in 42 (89%) responders versus 26 (59%) nonresponders ($p = 0.001$; assay sensitivity, 89%; negative predictive value, 78%). Moreover, 22 (47%) responders compared with eight (18%) nonresponders had a combination of peak post-treatment titers >800 and peak antibody fold change >8 ($p = 0.004$; assay specificity, 82%; positive predictive value, 73%). A majority of responders continued to have post-treatment antibody titers >800 after the first 6 mo of therapy. In conclusion, serum antiadenovirus antibody quantification may serve as a novel predictive marker for nadofaragene firadenovec response durability. Future studies will focus on large-scale validation and clinical utility of the assay.

Patient summary: This study reports on a planned secondary analysis of a phase 3 multicenter clinical trial that established the benefit of nadofaragene firadenovec, a novel intravesical gene therapeutic, for the treatment of patients with bacillus Calmette-Guérin (BCG)-unresponsive high-risk non–muscle-invasive bladder cancer. Prospective assessment of serum anti–human adenovirus type-5 antibody levels of patients in this trial indicated that a combination of post-treatment titers and fold change from baseline can predict treatment efficacy. While this merits additional validation, our findings suggest that serum antiadenovirus antibody levels can serve as an important predictive marker for the durability of therapeutic response to nadofaragene firadenovec.

Intravesical bacillus Calmette-Guérin (BCG) is frontline therapy for high-risk non–muscle-invasive bladder cancer (NMIBC) [1]. Although 80% of patients respond to BCG, 20–50% will eventually recur or progress [2]. Pembrolizumab is approved for BCG-unresponsive carcinoma in situ (CIS) based on a phase 2 study reporting 19% 12-mo complete response rate (CRR), but is associated with 13% grade 3–4 drug-related adverse events (DAEs), including 21% immune-mediated DAEs [3]. Nadofaragene firadenovec is a recombinant adenovirus vector plus polyamide surfactant capable of expressing therapeutic *IFNα* transgene in treated urothelium [4–7]. We reported a first-of-its-kind phase 3 multicenter trial of intravesical nadofaragene firadenovec in BCG-unresponsive NMIBC with 60% CRR within 3 mo of the first dose in the efficacy population, which was maintained in 51% of responders at 12 mo [8]. Administered intravesically once every 3 mo, it was associated with 4% grade 3 DAEs.

Of the complete responders in the phase 2 trial, 71% had elevated serum anti–human adenovirus type-5 (anti–HAdV-5) antibody titers [7]. Given the association of antibody levels with adenovirus-mediated gene therapy response in gliomas [9], we investigated whether anti–HAdV-5 levels predicted durable response to nadofaragene firadenovec in the phase 3 trial. A total of 157 patients met the trial criteria and received at least one dose (Supplementary Fig. 1). Therapy was administered every 3 mo after pretreatment evaluation for high-grade recurrence. Peripheral blood was obtained at baseline and every 3 mo thereafter for patients responding to therapy. Antibody titers were determined by a validated quantitative enzyme-linked immunosorbent assay (Supplementary material, Methods and Results). Follow-up was until trial's primary endpoint of 12 mo after the first dose or development of high-grade recurrence, whichever occurred first. The goal was to determine whether antibody levels at baseline or post-treatment predicted durable response.

Ninety-one (58% of eligible) safety population patients had baseline and at least one post-treatment titer available, and were included for analysis. All patients had urothelial carcinoma without histological variants, of whom 57 (63%) had CIS with or without Ta/T1 disease (CIS subcohort) and 34 (37%) had high-grade Ta/T1 tumors without CIS (high-grade Ta/T1 subcohort). The median age was 71 (interquartile range, 66–77) yr. Forty-seven (52%) patients remained high-grade recurrence free at 12 mo (responders), while 44 (48%) patients developed high-grade recurrence or disease progression at or before the 12-mo primary endpoint (nonresponders).

Antibody titers at baseline, after treatment, and at peak and associated fold changes were determined on a continuous scale (Fig. 1A–E). Thirty-two (68%) responders and 40 (91%) nonresponders achieved peak titers within 6 mo of starting treatment (Fig. 1F and G), with the median fold change also peaking at 6 mo in both subcohorts (Supplementary Fig. 2). As adenovirus seropositivity is widely

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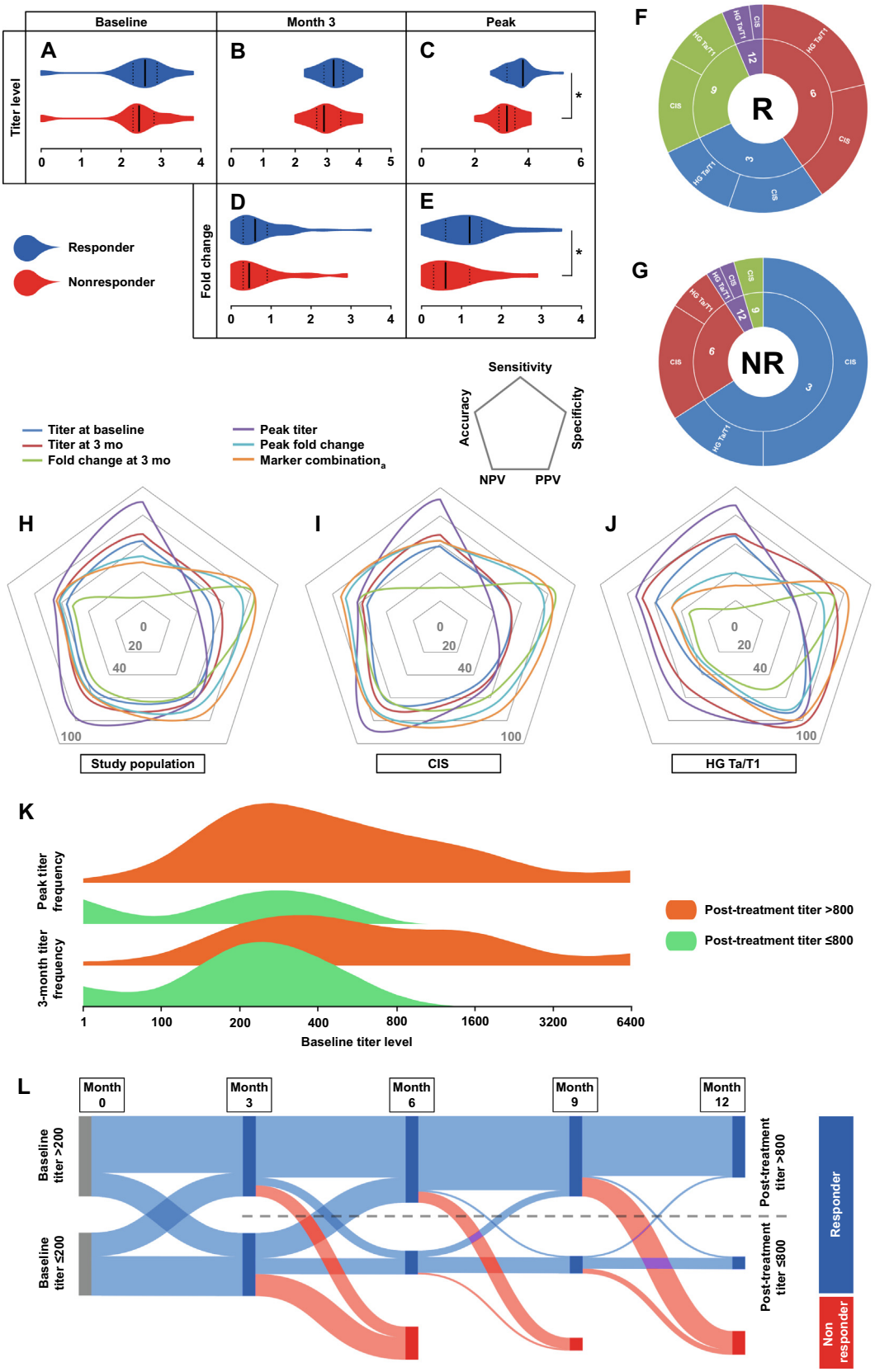

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Table 1 – Distribution of antiadenoviral antibody titers and fold changes from baseline, and relative risk of nondurable response to nadofaragene firadenovec treatment in the study population (n = 91)

	Distribution			Relative risk of nondurable response	
	Responders n (%) [a]	Nonresponders n (%) [a]	p value [b]	Hazard ratio (95% CI)	p value [c]
Study population, n (row %)	47 (52)	44 (48)			
Titer at baseline			0.26		0.41
>200	29 (62)	22 (50)		1.00 (Reference)	
≤200	18 (38)	22 (50)		1.28 (0.71–2.32)	
Titer at 3 mo			0.026		0.067
>800	30 (67)	19 (43)		1.00 (Reference)	
≤800	15 (33)	25 (57)		1.75 (0.96–3.18)	
Fold change at 3 mo			0.64		0.61
>8	10 (22)	8 (18)		1.00 (Reference)	
≤8	35 (78)	36 (82)		1.22 (0.57–2.62)	
Peak titer			0.001		<0.001
>800	42 (89)	26 (59)		1.00 (Reference)	
≤800	5 (11)	18 (41)		2.98 (1.62–5.50)	
Peak fold change			0.020		0.024
>8	24 (51)	12 (27)		1.00 (Reference)	
≤8	23 (49)	32 (73)		2.16 (1.11–4.19)	
Marker combination [d]			0.004		0.005
Favorable	22 (47)	8 (18)		1.00 (Reference)	
Unfavorable	25 (53)	36 (82)		3.00 (1.39–6.48)	

CI = confidence interval.
[a] Column % unless otherwise indicated.
[b] p value based on Pearson's chi-square test except when any expected cell value was <5, where Fisher's exact test was used instead.
[c] p value based on Cox regression.
[d] Favorable defined as a combination of peak antibody titer >800 and peak antibody fold change level >8. Patients not meeting both criteria were designated as unfavorable.

prevalent, we evaluated whether pre-existing immunity conferred a therapeutic advantage. While there was no difference in baseline titers between the treatment response groups, responders had higher peak titers (p < 0.001) and peak fold change (p = 0.009) compared with nonresponders (Supplementary Table 1). Baseline and post-treatment antibody titer cutoffs were evaluated for their ability to predict durable response (Supplementary Fig. 3). Optimal cutoffs were determined by maximizing the area under the receiver operating characteristic curve. This is clinically relevant in BCG-unresponsive NMIBC to maximize sensitivity (ie, identifying high-risk patients who may have durable response) and specificity (ie, identifying patients with impending failure who likely need alternate therapy). A baseline titer cutoff of 200 was unable to differentiate between responders and nonresponders (Table 1). However, a 3-mo post-treatment titer of >800 was associated with durable response (p = 0.026). Upon assessing peak post-treatment antibody levels, 42 (89%) responders had titers >800 compared with 26 (59%) nonresponders (p = 0.001; Table 1). Lower peak titers were associated with a higher risk of nondurable response (p < 0.001; Table 1). Sensitivity, negative predictive value, and accuracy of this assay in the study population were 89%, 78%, and 66%, respectively (Fig. 1H). Performance metrics were also notable in the CIS and high-grade Ta/T1 subcohorts (Supplementary Tables 2 and 3; Fig. 1I and J; Supplementary material, Results). Twenty-four (51%) responders had peak fold change >8 from baseline compared with 12 (27%) nonresponders (p = 0.020), with a higher risk of nondurable response with peak fold change ≤8 (p = 0.024; Table 1).

Given the markers' individual discriminative abilities, patients with peak titer >800 and peak fold change >8 were classified as favorable, and those not meeting these criteria were designated as unfavorable. Twenty-two (47%) responders were classified as favorable compared with only eight (18%) nonresponders (p = 0.004; Table 1). Of the nonresponders in the favorable subgroup, five (63%) recurred at the 12-mo evaluation. The unfavorable subgroup was associated with an elevated risk of nondurable response (p =

Fig. 1 – Anti–human adenovirus type-5 antibody titers in patients with bacillus Calmette-Guérin–unresponsive, high-risk, non–muscle-invasive bladder cancer. Distributions of log_{10}-transformed antibody titer levels between responders (blue) and nonresponders (red) at (A) baseline, (B) 3 mo after treatment, and (C) post-treatment peak, with corresponding log_{10}-transformed fold change differences compared with baseline at (D) 3 mo after treatment and (E) post-treatment peak. Solid and dotted lines indicate median and interquartile range, respectively. Proportions of (F) responders and (G) nonresponders reaching peak serum antibody titers at 3 (blue), 6 (red), 9 (green), and 12 (purple) mo following treatment with nadofaragene firadenovec, stratified by those in the CIS and high-grade Ta/T1 subcohorts. Performance metrics of baseline and various post-treatment antibody titers and fold change levels in the (H) entire study population, (I) carcinoma in situ subcohort, and (J) high-grade Ta/T1 subcohort. (K) Frequencies of patients with 3-mo (lower pair) and peak (upper pair) post-treatment antibody titers >800 (orange) and ≤800 (green), stratified by their corresponding baseline antibody titer levels (on *X* axis). (L) Relative proportion of patients in the study population initially stratified by baseline antibody titers, who were deemed responders (blue) and nonresponders (red) upon clinical evaluation for recurrence of high-grade disease at months 3, 6, 9, and 12. Responders are further stratified based on post-treatment antibody titers. Thickness of colored curves corresponds to the relative proportion of the respective originating node. CIS = carcinoma in situ subcohort; HG Ta/T1 = high-grade Ta/T1 subcohort; NPV = negative predictive value; NR = nonresponders; PPV = positive predictive value; R = responders. [a] A marker combination status where patients with peak antibody titer >800 and peak antibody fold change level >8 were deemed favorable, and the remainder were designated as unfavorable. * p < 0.010.

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0.005; Table 1). Specificity and positive predictive value of marker combination in the study population were 82% and 73%, respectively (Fig. 1H). Performance metrics were also superior in the CIS subcohort (Supplementary material, Results).

Exploratory analyses revealed no association between the time from the last tumor resection to the first dose and first post-treatment titers at 3 mo (Supplementary Fig. 4). Low baseline levels were associated with low post-treatment titers ($p < 0.001$; Supplementary Table 4), and lower frequency of 3-mo and peak post-treatment titers >800 (Fig. 1K). Conversely, higher baseline levels corresponded with higher frequency of post-treatment titers >800. Among subgroups stratified by baseline and post-treatment titers, the highest crossover frequency between low- and high-titer subgroups occurred in the first 6 mo of therapy, after which the highest proportion of responders continued to have post-treatment titers >800 (Fig. 1L).

IFNα antitumor activity is mediated through direct cytotoxicity, inhibiting cellular proliferation and angiogenesis, and immune activation [4]. However, mechanisms for anti–HAdV-5 increase in durable responders by nadofaragene firadenovec are less well understood, and may partly be associated with anti–HAdV-5 immunodiversity at baseline and patients' subsequent post-treatment responses [10]. While the use of a novel therapeutic precludes independent validation, the rigor of our results arises from the standardized, clinically validated, and reproducible assay used to develop these predictive metrics.

In summary, we describe anti–HAdV-5 titers as a novel therapeutic efficacy marker for nadofaragene firadenovec in the setting of a prospective clinical trial. While further validation and clinical utility assessments are necessary, these data suggest that anti–HAdV-5 titer metrics can predict durable treatment responses and identify patients who may benefit from other bladder-preservation strategies. Such efforts can identify efficacy biomarkers that improve patient selection for emerging therapies against BCG-unresponsive NMIBC.

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Study concept and design: Mitra, Boorjian, Ylä-Herttuala, Sawutz, Parker, McConkey, Dinney.
Acquisition of data: Boorjian, Alemozaffar, Konety, Shore, Gomella, Kamat, Bivalacqua, Montgomery, Lerner, Busby, Poch, Crispen, Steinberg, Schuckman, Downs, Svatek, Mashni Jr, Lane, Guzzo, Bratslavsky, Karsh, Woods, Brown, Canter, Luchey, Lotan, Krupski, Inman, Williams, Cookson, Keegan, Andriole Jr, Sankin, O'Donnell, Dinney.
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