

Summary

JANUARY 2021

WHAT IS BLADDER CANCER?

Bladder cancer is the sixth most common cancer in the United States, with approximately 80,000 new cases each year and 17,700 deaths. For most patients when first diagnosed, the cancer is confined to the bladder (non-muscle invasive bladder cancer, NMIBC) and is treated with surgical removal of visible tumor and local instillation of medicine into the bladder (intravesical therapy). For those at high risk of recurrence/progression, an intravesical therapy called BCG is recommended.

However, for those with BCG-unresponsive NMIBC, surgery may be recommended to entirely remove the bladder (cystectomy). Irrespective of the specific treatment, bladder cancer can have a large effect on patients' lives; this can include the side effects of treatments, the time and costs of surveillance, and the morbidity and effects on quality of life of cystectomy.

TREATMENT OPTIONS

- **Nadofaragene firadenovec (Adstiladrin®)** uses a nonreplicating recombinant adenovirus vector that encodes the human interferon alfa-2b gene with Syn3, a polyamide surfactant, to enhance transfer into cancer cells. It is instilled every three months. In May 2020, the US Food and Drug Administration (FDA) issued a Complete Response Letter requesting additional information regarding manufacturing.
- **Oportuzumab monatox (Vicineum®)** is a recombinant fusion protein with a humanized antiepithelial cell adhesion molecule (EpCAM) antibody linked to Pseudomonas exotoxin A that binds to the cancer cell and then releases the toxin into the cell, inducing cell death. It is instilled twice a week for six weeks, then weekly for six weeks and then every two weeks for up to two years. A rolling Biologics License Application (BLA) was submitted in December 2019.

* Originally published in December 2020, this report was updated on January 15, 2021. A data entry error affected model results regarding nadofaragene firadenovec when used in the Ta/T1 population. Results have been corrected in this update, including a revised health-benefit price benchmark for nadofaragene firadenovec.

KEY REPORT FINDINGS

- Nadofaragene and oportuzumab demonstrated rates of complete response and high grade recurrence free survival better than historical results in single-arm phase III trials. The evidence has significant limitations, and no firm estimate of net health benefit versus best supportive care was able to be determined for either nadofaragene firadenovec or oportuzumab monatox; the evidence is also inadequate to enable a clear comparison of these treatments to each other or to other active treatments.
- Based on the estimates derived from single-arm trials of patient benefits from delay of metastasis and need for cystectomy, ICER calculates an annual health benefit price benchmark (HBPB) range of approximately \$92,800-\$200,900 for both agents; the underlying limitations in the clinical evidence create substantial uncertainty in these price benchmarks. These HBPB ranges should be viewed as an upper bound on pricing, because ICER's cost-effectiveness model is comparing these therapies to best supportive care. Most clinicians caring for patients with BCG-unresponsive NMIBC who choose not to have cystectomy would likely use treatments with at least some short-term efficacy.

KEY POLICY RECOMMENDATIONS

- Manufacturers should acknowledge that single-arm trials usually fail to provide the kind of evidence that is needed to help patients, clinicians, and insurers understand the comparative clinical effectiveness and value of new treatments.
- Regulators have an important role to play in how new therapeutics enter clinical practice. The lack of a clear consensus on "standard care" for BCG-unresponsive NMIBC provides no justification for the FDA's failure to require randomized trials comparing emerging therapies to active regimens.
- Patient groups advocating for bladder cancer research and for patients with bladder cancer have played an essential role in bringing forward important new advances in care. These groups should continue their efforts to encourage innovation while pushing life science companies to generate better evidence to guide patient and clinician decision-making.

Clinical Analyses

How strong is the evidence that these therapies improve outcomes in patients with bladder cancer?

Summary of Evidence Ratings for Nadofaragene Firadenovec and Oportuzumab Monatox

ICER EVIDENCE RATINGS

Intervention	Tumor Grade Evidence Rating	ICER Evidence Rating
Nadofaragene <i>Firadenovec</i> vs. best supportive care	All	C++
Oportuzumab Monatox vs. best supportive care	All	C++
Nadofaragene <i>Firadenovec</i> vs. Oportuzumab Monatox	All	I
Nadofaragene <i>Firadenovec</i> vs. Pembrolizumab	CIS ± HG Ta/T1	I
Oportuzumab Monatox vs. Pembrolizumab	CIS ± HG Ta/T1	I
Nadofaragene <i>Firadenovec</i> vs. Gemcitabine ± Docetaxel	All	I
Oportuzumab Monatox vs. Gemcitabine ± Docetaxel	All	I

CIS: carcinoma in situ, HG: high grade, Ta: non-invasive papillary carcinoma, T1: tumor invading sub-epithelial connective tissue (lamina propria)

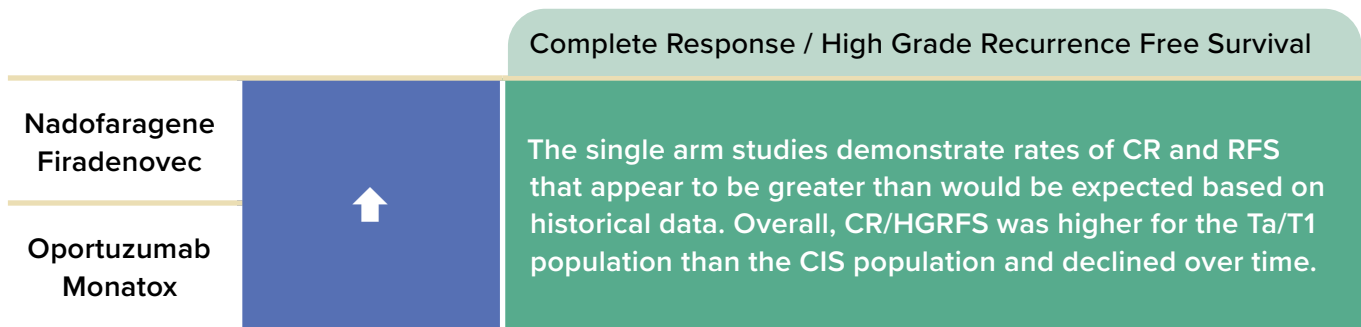
Significant limitations exist in the available clinical trial evidence, but available evidence suggests that both nadofaragene firadenovec and oportuzumab monatox are at least comparable to best supportive care and may provide a net health benefit ranging from small to moderate (“C++”). The current evidence is insufficient (“I”) to compare these interventions to each other or to commonly used active treatment options gemcitabine ± docetaxel and pembrolizumab.

Clinical Analyses (continued)

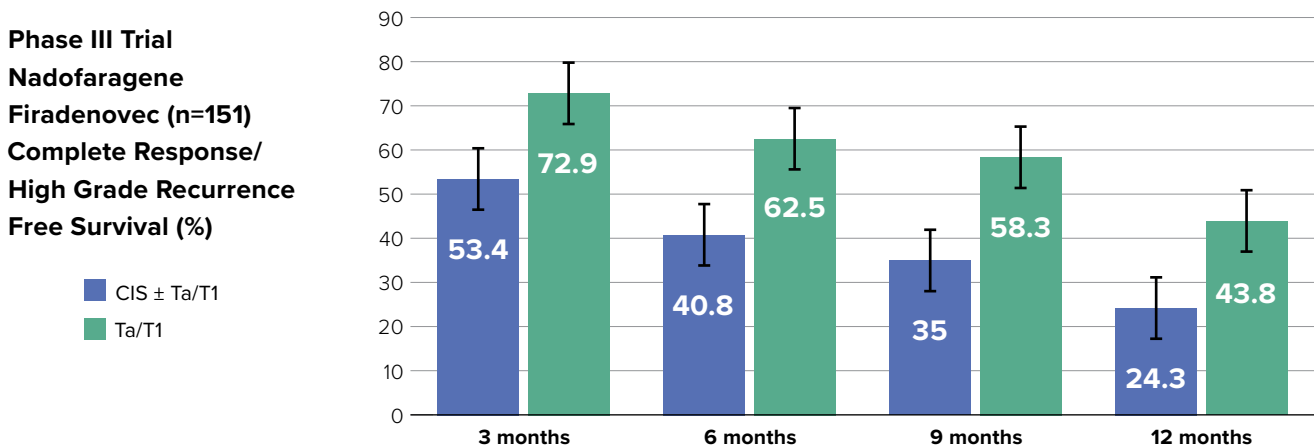
KEY CLINICAL BENEFITS STUDIED IN CLINICAL TRIALS

How effective are these therapies?

The primary efficacy endpoints in all trials of nadofaragene firadenovec, oportuzumab monatox, and pembrolizumab were complete response (CR) and high-grade recurrence free survival (HGRFS) at pre-specified time points after initial evaluation. The single arm studies of nadofaragene firadenovec and oportuzumab monatox demonstrate rates of CR and RFS that appear to be greater than would be expected based on historical data. Overall, CR/HGRFS was higher for the Ta/T1 population than the CIS population and declined over time. Though outcomes of nadofaragene firadenovec and oportuzumab monatox show response rates that are similar to or better than currently available treatments, efficacy over longer time periods remain uncertain.



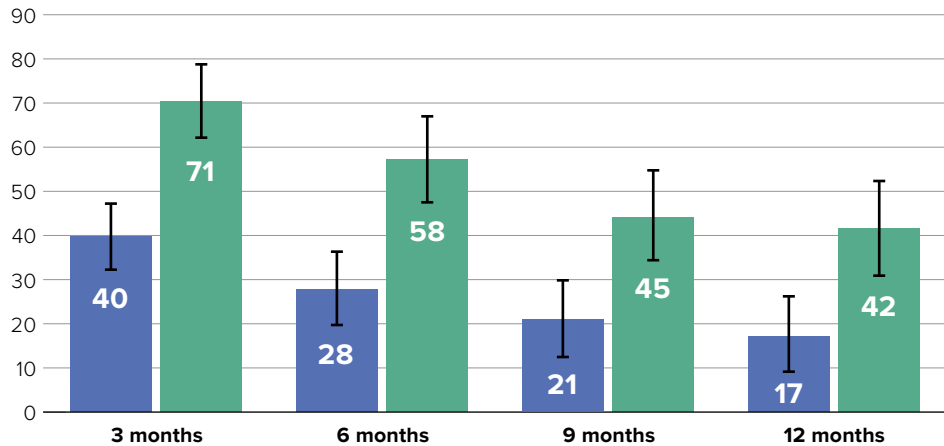
Differences in study population, design and outcomes were felt to be too great to directly compare results of the new agents to each other and to other therapies. Thus, trial results are presented for each separately.



Clinical Analyses (continued)

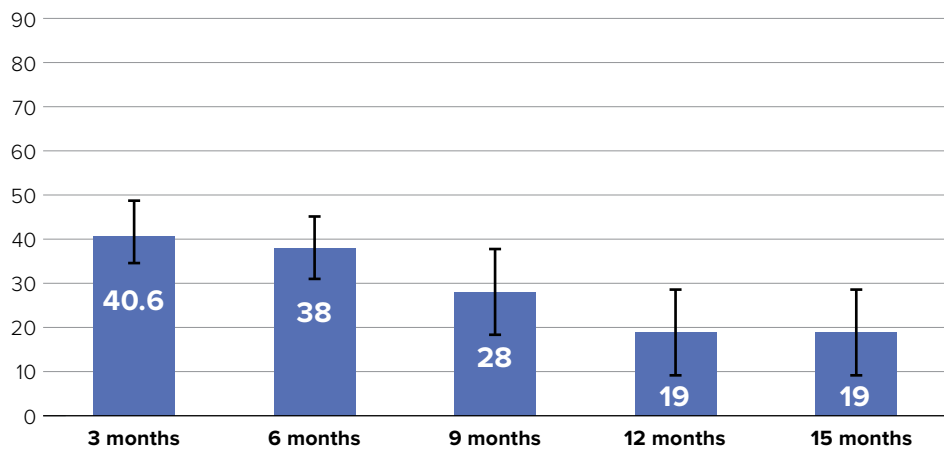
Phase III Trial
Oportuzumab Monatox
(n=127)
**Complete Response/
 High Grade Recurrence
 Free Survival (%)**

■ CIS ± Ta/T1
 ■ Ta/T1



Phase II Trial
Pembrolizumab (n=96)
**Complete Response
 (%), CIS ± Ta/T1**

■ CIS ± Ta/T1



HARMS

Nadofaragene firadenovec: In the Phase III trial, 146 (93%) reported any treatment-emergent adverse event (TEAE), of which 29 (18%) were grade 3-5 and 14 (9%) were serious. The most commonly reported drug-related AE was irritative voiding symptoms. Serious events included one case each of syncope, sepsis, and hematuria.

Oportuzumab monatox: As of the 12-month data output (05/29/2019 data cut-off) for the phase III trial, 117 patients (88%) reported any TEAE. The most common TEAEs were urinary tract infection (32%), pain or burning on urination (26%), hematuria (25%), and urinary frequency (17%). The most common serious TEAEs were acute kidney injury (2%), intestinal obstruction (2%), and serious hematuria or urinary tract infection (4%). One death was also reported.

Clinical Analyses (continued)

Pembrolizumab: One hundred two patients were evaluated in the safety population of the phase II Keynote-057 trial. Ninety-nine (97.1%) patients reported experiencing any AE with the majority being grade 1 to 2 in severity. Two deaths occurred in patients receiving pembrolizumab during the trial, one due to respiratory failure due to MRSA pneumonia and one due to metastatic pancreatic cancer. Twenty-one (20.6%) patients reported any immune-mediated AEs or infusion reactions, with 3 (2.9%) classified as grade 3-5 and 5 (4.9%) classified as serious. Immune-mediated AEs and infusion reactions included events such as hypothyroidism, hyperthyroidism, pneumonitis, adrenal insufficiency, and colitis.

Gemcitabine ± Docetaxel: Harms of gemcitabine with and without docetaxel were not reported consistently and estimates varied. The most reported AEs were dysuria (9-30%), hematuria (3-28%), urinary tract infection (3-6%). Discontinuation or alteration in treatment schedule due to AEs were reported by 9-12%.

SOURCES OF UNCERTAINTY

Lack of comparative data: for patients with BCG-unresponsive NMIBC, nadofaragene firadenovec and oportuzumab monatox were evaluated in single-arm trials without a placebo or standard treatment group. Differences in study population, design and outcomes were felt to be too great to compare results. The lack of comparative data limits the ability to compare these new agents to each other and other therapies.

Inconsistent clinical trial definitions: studies also defined patients who had failed BCG differently. Heterogeneous patient populations in terms of the proportion who are BCG-refractory, BCG-relapsing, BCG-intolerant, or BCG-unresponsive can cause difficulty in comparing treatment outcomes among trials. Moreover, the specific prior treatments received, and their intensity may also lead to differences among studies.

Inconsistent clinical trial endpoints: as with differences among trials in terms of study population characteristics, the nature of the outcome assessed can impact the ability to compare results across trials. The primary outcome of nadofaragene firadenovec and oportuzumab monatox was complete response assessed at similar time intervals, but even here, the final outcome time point required a biopsy for all patients in the nadofaragene firadenovec trial, but not for the oportuzumab monatox or pembrolizumab trials.

Economic Analyses

LONG-TERM COST-EFFECTIVENESS

Do these treatments meet established thresholds for long-term cost-effectiveness based on placeholder prices?

Incremental Cost-Effectiveness Ratios for Nadofaragene Firadenovec, Oportuzumab Monatox Compared, Pembrolizumab, and Gemcitabine ± Docetaxel Compared to the Hypothetical Treatment in Patients with CIS ± Ta/T1

Treatment	Comparator	Cost per QALY Gained	Cost per evLYG	Cost per LYG	Cost per Year in Progression-Free State
Results Based on Prospective Studies of Instilled Therapies					
Nadofaragene Firadenovec*	Hypothetical Treatment	\$151,000	\$135,000	\$135,000	\$100,000
Oportuzumab Monatox	Hypothetical Treatment	\$382,000	\$343,000	\$367,000	\$281,000
Results Based on Prospective Studies of Systemic Therapy					
Pembrolizumab	Hypothetical Treatment	\$114,000	\$103,000	\$102,000	\$76,000
Results Based on Retrospective Studies of Instilled Therapies					
Gemcitabine ± Docetaxel	Hypothetical Treatment	Dominates	Dominates	Dominates	Dominates

evLYG: equal value life year gained, LYG: life year gained, QALY: quality-adjusted life year

*Price for nadofaragene firadenovec was a placeholder price based on annual price of pembrolizumab

Economic Analyses (continued)

Incremental Cost-Effectiveness Ratios for Nadofaragene Firadenovec, Oportuzumab Monatox and Gemcitabine ± Docetaxel Compared to the Hypothetical Treatment in Patients with High Grade Ta/T1 Alone

Treatment	Comparator	Cost per QALY Gained	Cost per evLYG	Cost per LYG	Cost per Year in Progression-Free State
Results Based on Prospective Studies of Instilled Therapies					
Nadofaragene Firadenovec*	Hypothetical Treatment	\$93,000	\$85,000	\$87,000	\$65,000
Oportuzumab Monatox	Hypothetical Treatment	\$123,000	\$111,000	\$117,000	\$88,000
Results Based on Retrospective Studies of Instilled Therapies					
Gemcitabine ± Docetaxel	Hypothetical Treatment	Dominates	Dominates	Dominates	Dominates

evLYG: equal value life year gained, LYG: life year gained, QALY: quality-adjusted life year

*Price for nadofaragene firadenovec was a placeholder price based on annual price of pembrolizumab

Economic Analyses (continued)

HEALTH-BENEFIT PRICE BENCHMARKS

What is a fair price for these therapies based on its value to patients and the health care system?

Neither drug has received FDA approval yet, so there is no known US market price. Based on the available data from single-arm trials suggesting delay in metastasis and requirement for cystectomy compared to historical estimates of outcomes with best supportive care, ICER's recommended health-benefit price benchmark ranges are \$158,600-\$262,000 per year for nadofaragene firadenovec and \$92,800-\$162,100 per year for oportuzumab monatox. These HBPB ranges should be viewed as an upper bound on pricing, because ICER's cost-effectiveness model is comparing these therapies to best supportive care. Most clinicians caring for patients with BCG-unresponsive NMIBC who choose not to have cystectomy would likely use treatments with at least some short-term efficacy.

POTENTIAL SHORT-TERM BUDGET IMPACT

How many patients can be treated before crossing ICER's \$819 million budget impact threshold based on placeholder prices?

Nadofaragene firadenovec: 52% of eligible patients could be treated before crossing ICER's potential budget impact threshold of \$819 million per year.

Oportuzumab monatox: 53% of eligible patients could be treated before crossing ICER's potential budget impact threshold of \$819 million per year.

Voting Results

The Midwest CEPAC deliberated on key questions raised by ICER's report at a public meeting on November 20, 2020. The results of the votes are presented below. More detail on the voting results is provided in the [full report](#).

CLINICAL EVIDENCE

Patient population: adults with BCG-unresponsive, high-risk NMIBC (CIS ± Ta/T1 or non-CIS with high grade Ta/T1)

- A majority of panelists found the evidence is adequate to demonstrate that the net health benefit of nadofaragene firadenovec is superior to that provided by best supportive care.
- A majority of panelists found the evidence is adequate to demonstrate a net health benefit of oportuzumab monatox to that provided by best supportive care.
- All panelists found that the evidence is not adequate to distinguish the net health benefit provided by nadofaragene firadenovec when compared to oportuzumab monatox.
- All panelists found the evidence is not adequate to demonstrate a superior net health benefit of nadofaragene firadenovec over gemcitabine with or without docetaxel.
- All panelists found the evidence is not adequate to demonstrate a superior net health benefit of oportuzumab monatox over gemcitabine with or without docetaxel.

Patient population: adults with BCG-unresponsive, high-risk NMIBC with CIS ± Ta/T1

- All panelists found the evidence is not adequate to demonstrate a superior net health benefit of nadofaragene firadenovec over systemic pembrolizumab.
- A majority of panelists found the evidence is not adequate to demonstrate a superior net health benefit of oportuzumab monatox over systemic pembrolizumab.

LONG-TERM VALUE FOR MONEY

- We did not conduct any long-term for money votes because neither drug has received FDA approval yet (so there are no known US market prices).

OTHER BENEFITS AND CONTEXTUAL CONSIDERATIONS

ICER asks panelists to vote on whether specific potential other benefits, disadvantages, and contextual considerations are important to weigh in judging the long-term value for money of the intervention.

For nadofaragene firadenovec, a majority of the panel voted:

- Economic model assumptions were neither too optimistic nor pessimistic.
- Nadofaragene firadenovec offers a new mechanism of action compared to that of other treatments.
- Nadofaragene firadenovec's relative simplicity of regimen is likely to result in higher real-world adherence and better outcomes relative to other treatment options that require more frequent clinician visits.

For oportuzumab monatox, a majority of the panel voted :

- Economic model assumptions were neither too optimistic nor pessimistic.
- Oportuzumab monatox offers a new mechanism of action compared to that of other treatments.

Policy Recommendations

For Patient Advocacy Organizations

- Patient groups advocating for bladder cancer research and for patients with bladder cancer have played an essential role in bringing forward important new advances in care. These groups should continue their efforts to encourage innovation while pushing life science companies to generate better evidence to guide patient and clinician decision-making.
- Patient groups should fully embrace their power to speak explicitly about the impact of the high cost of treatments for BCG-unresponsive NMIBC.
 - General statements of concern about “cost” shifts the focus subtly away from prices, which is consistent with the interests of the life science industry. Doing so deflects from the reality that drug makers have the power to set prices in the United States and the result produces affordability concerns for health systems, financial toxicity for patients and families, and barriers to the ability of patients to gain access to optimal clinical care. Bladder cancer patient groups should be willing to name the problem and bear witness to the harms that excessive prices for new therapies cause.

For Payers

- Prior authorization criteria should be based on clinical evidence, specialty society guidelines, and input from clinical experts and patient groups. The process for authorization should be clear and efficient for providers.

For Providers

- Providers should engage in a shared decision-making process with their patients and not let their treatment recommendations be unduly swayed by the perverse incentives that often pay clinicians more for administering more expensive treatment options. In bladder cancer this is particularly relevant given the dramatic price difference between chemotherapy and the prices expected for the emerging agents nadofaragene firadenovec and oportuzumab monatox.

Clinical and Specialty Societies

- Bladder cancer specialists and specialty societies should rapidly move to update guideline recommendations to address the role in therapy of these new treatment options for BCG-unresponsive NMIBC.

For Manufacturers and Clinical Researchers

- Manufacturers should acknowledge that single-arm trials usually fail to provide the kind of evidence that is needed to help patients, clinicians, and insurers understand the comparative clinical effectiveness and value of new treatments.
 - Manufacturers developing new treatments for BCG-unresponsive NMIBC should therefore use randomized trials as the basis for regulatory approval. Where this has not been done, manufacturers should sponsor real-world comparative studies of their therapies that can help evaluate a broad set of patient-relevant outcomes including quality of life, work and disability status, and overall mortality.

Policy Recommendations (continued)

- Manufacturers should set prices for new therapies based on their demonstrated added clinical value over lower-cost clinically appropriate regimens. Leapfrogging these lower-cost regimens and setting prices in conjunction with higher-cost options adds to the growing financial toxicity of oncology care for patients today and in the future.
- Researchers [and manufacturers] should compare nadofaragene firadenovec and oportuzumab monatox to other therapies in randomized trials of patients with BCG-NMIBC.
- Researchers [and manufacturers] should develop comparative trials of BCG-unresponsive NMIBC that assess whether new medications have a lower risk of progression to cystectomy and other important patient outcomes over time.

Regulators

- Regulators have an important role to play in how new therapeutics enter clinical practice. The lack of a clear consensus on “standard care” for BCG-unresponsive NMIBC provides no justification for the FDA’s failure to require randomized trials comparing emerging therapies to active regimens.

About ICER

The Institute for Clinical and Economic Review ([ICER](https://www.icer.org)) is an independent nonprofit research institute that produces reports analyzing the evidence on the effectiveness and value of drugs and other medical services. ICER's reports include evidence-based calculations of prices for new drugs that accurately reflect the degree of improvement expected in long-term patient outcomes, while also highlighting price levels that might contribute to unaffordable short-term cost growth for the overall health care system.

ICER's reports incorporate extensive input from all stakeholders and are the subject of public hearings through three core programs: the California Technology Assessment Forum ([CTAF](https://www.ctaf.org)), the Midwest Comparative Effectiveness Public Advisory Council ([Midwest CEPAC](https://www.midwestcepac.org)) and the New England Comparative Effectiveness Public Advisory Council ([New England CEPAC](https://www.newenglandcepac.org)). These independent panels review ICER's reports at public meetings to deliberate on the evidence and develop recommendations for how patients, clinicians, insurers, and policymakers can improve the quality and value of health care.

For more information about ICER, please visit ICER's website (www.icer.org).