Nadofaragene Firadenovec and Oportuzumab Monatox for BCG-Unresponsive, Non-Muscle Invasive Bladder Cancer: Effectiveness and Value

Final Report

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Prepared for:

New evidence regarding treatments and therapies gets published on an ongoing basis. ICER reached out to key stakeholders included in this review 12 months after the publication of this report giving them an opportunity to submit public comments regarding new relevant data or information on coverage that they wish to highlight. Their statements can be found here. ICER has launched ICER Analytics to provide stakeholders an opportunity to work directly with ICER models and examine how changes in parameters would affect results.
You can learn more about ICER Analytics here.

September 7, 2021 Update: In August 2021, the United States Food and Drug Administration issued a Complete Response Letter for oportuzumab monatox. Additionally, published reports stated that there were problems with the conduct of a clinical trial of the drug as well as reporting of safety events. As such, this ICER report should be considered **no longer current with respect to oportuzumab monatox**.

January 15, 2021 Update: A data entry error affected model results regarding nadofaragene firadenovec when used in the Ta/T1 population. Results have been corrected in this update, and include a revised Health-Benefit Price Benchmark (HBPB) range for nadofaragene firadenovec.

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Steven Atlas served as the lead author for the report. Molly Beinfeld led the systematic review and authorship of the comparative clinical effectiveness section in collaboration with Avery McKenna and Kanya Shah. Steven Atlas and Molly Beinfeld authored the chapter describing what ICER learned from patients (Chapter 2 Patient Perspectives). Daniel Touchette was responsible for the development of the cost-effectiveness model with support from Mrinmayee Joshi, Ryan Rodriguez, and Shani Patel. Rick Chapman was responsible for oversight of the cost-effectiveness analyses and developed the budget impact model. Monica Frederick authored the section on clinical guidelines in collaboration with Maggie O'Grady. David Rind and Steven Pearson provided methodologic guidance on the clinical and economic evaluations.

About ICER

The Institute for Clinical and Economic Review (ICER) is an independent non-profit research organization that evaluates medical evidence and convenes public deliberative bodies to help stakeholders interpret and apply evidence to improve patient outcomes and control costs. Through all its work, ICER seeks to help create a future in which collaborative efforts to move evidence into action provide the foundation for a more effective, efficient, and just health care system. More information about ICER is available at https://icer.org/.

The funding for this report comes from government grants and non-profit foundations, with the largest single funder being Arnold Ventures. No funding for this work comes from health insurers, pharmacy benefit managers, or life science companies. ICER receives approximately 19% of its overall revenue from these health industry organizations to run a separate Policy Summit program, with funding approximately equally split between insurers/PBMs and life science companies. Merck is the only life science company relevant to this review who participates in this program. For a complete list of funders and for more information on ICER's support, please visit https://icer.org/who-we-are/independent-funding/.

For drug topics, in addition to receiving recommendations from the public, ICER scans publicly available information and also benefits from a collaboration with IPD Analytics, an independent organization that performs analyses of the emerging drug pipeline for a diverse group of industry stakeholders, including payers, pharmaceutical manufacturers, providers, and wholesalers. IPD provides a tailored report on the drug pipeline on a courtesy basis to ICER but does not prioritize topics for specific ICER assessments.

About Midwest CEPAC

The Midwest Comparative Effectiveness Public Advisory Council (Midwest CEPAC) – a core program of ICER – provides a public venue in which the evidence on the effectiveness and value of health care services can be discussed with the input of all stakeholders. Midwest CEPAC seeks to help patients, clinicians, insurers, and policymakers interpret and use evidence to improve the quality and value of health care.

The Midwest CEPAC is an independent committee of medical evidence experts from across the Midwest, with a mix of practicing clinicians, methodologists, and leaders in patient engagement and advocacy. All Council members meet strict conflict of interest guidelines and are convened to discuss the evidence summarized in ICER reports and vote on the comparative clinical effectiveness and value of medical interventions. More information about Midwest CEPAC is available at https://icer.org/who-we-are/people/independent-appraisal-committees/midwest-comparative-effectiveness-public-advisory-council-m-cepac/.

The findings contained within this report are current as of the date of publication. Readers should be aware that new evidence may emerge following the publication of this report that could potentially influence the results. ICER may revisit its analyses in a formal update to this report in the future.

The economic models used in ICER reports are intended to compare the clinical outcomes, expected costs, and cost-effectiveness of different care pathways for broad groups of patients. Model results therefore represent average findings across patients and should not be presumed to represent the clinical or cost outcomes for any specific patient. In addition, data inputs to ICER models often come from clinical trials; patients in these trials and provider prescribing patterns may differ in real-world practice settings.

In the development of this report, ICER's researchers consulted with several clinical experts, patients, manufacturers and other stakeholders. The following experts provided input that helped guide the ICER team as we shaped our scope and report. It is possible that expert reviewers may not have had the opportunity to review all portions of this report. None of these individuals is responsible for the final contents of this report, nor should it be assumed that they support any part of it. The report should be viewed as attributable solely to the ICER team and its affiliated researchers.

For a complete list of stakeholders from whom we requested input, please visit: https://icer.org/assessment/bladder-cancer-2020/.

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List of Acronyms and Abbreviations Used in this Report

AE	Adverse event
AHRQ	Agency for Healthcare Research and Quality
AUA	American Urological Association
BCG	Bacillus Calmette-Guerin
CIS	Carcinoma in situ
CR	Complete response
CT	Computed tomography
CTU	Computer tomography urography
EpCAM	Epithelial cell adhesion molecule
evLYG	Equal value life year gained
FACT-BI	Functional Assessment of Cancer Therapy – Bladder Cancer
FACT-G	Functional Assessment of Cancer Therapy – General
FDA	Food and Drug Administration
HG	High grade
HGRFS	High grade recurrence free survival
HRQoL	Health-related quality of life
LY	Life year
MIBC	Muscle invasive bladder cancer
NCCN	National Comprehensive Cancer Network
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NMIBC	Non-muscle invasive bladder cancer
PICOTS	Population, Intervention, Comparators, Outcomes, Timing, and Settings
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QALY	Quality-adjusted life year
RFS	Recurrence free survival
SAE	Serious adverse event
SUO	Society of Urologic Oncology
T1	Tumor invading sub-epithelial connective tissue (lamina propria)
T2	Muscle-invasive tumor
Ta	Non-invasive papillary carcinoma
Tis	Tumor in situ
TURBT	Transurethral resection of bladder tumor
UC	Usual care
US	United States
USPSTF	United States Preventive Services Task Force

Executive Summary

Background

Bladder cancer is the sixth most common cancer in the United States (US), with approximately 80,000 new cases each year and 17,700 deaths.[1,2] Bladder cancer usually presents with blood in the urine (hematuria) and can also have symptoms such as frequency, urgency, or pain when urinating.[3] For most patients when first diagnosed, the cancer is confined to the bladder and is treated with limited surgical removal and local instillation of medicine into the bladder (intravesical therapy). However, for those with more advanced disease or not responding to or tolerating intravesical therapy, surgery may be performed to entirely remove the bladder (cystectomy).[4,5] Irrespective of the specific treatment, bladder cancer can have a large effect on patients' lives; this can include the side effects of treatments given, the time and costs of surveillance, and the morbidity and effects on quality of life of cystectomy. The overall cost of health care for those with bladder cancer is estimated to be $4-5 billion annually in the US.[6]

Diagnosis of bladder cancer typically involves the direct examination of the lining of the bladder with a fiberoptic scope test, called a cystoscopy, that permits taking biopsy specimens. When first diagnosed, around 70% of bladder cancers are localized, non-muscle invasive bladder cancer (NMIBC). There are three types of NMIBC: 1) polyps extending from the lining into the bladder itself (Ta, about 70%); 2) flat, superficial growths (carcinoma in situ [CIS], about 10%); and 3) tumors growing below the superficial lining cells but not into the deeper muscular layer of the bladder wall (T1, about 20%).[7]

Primary treatment of NMIBC involves removal of visible cancer with transurethral resection of bladder tumor (TURBT) followed by intravesical therapy for those at increased risk for progression to muscle-invasive disease. Bacillus Calmette-Guerin (BCG), an attenuated live form of *Mycobacterium bovis*, is the standard initial intravesical therapy, but intravesical chemotherapy treatments are also used.[8] An initial course of therapy involves repeated instillations via a catheter into the bladder. If a response is seen, subsequent maintenance treatment is provided, usually on a less intense schedule.

Though the prognosis for NMIBC is good, and available treatment with BCG or other intravesical chemotherapy in addition to TURBT is effective, many patients will experience a recurrence.9 For those with BCG-unresponsive disease, meaning they have progression during treatment with BCG (refractory disease) or relapse soon after stopping therapy, current treatment includes use of other intravesical treatment, such as gemcitabine either alone or alternating with another chemotherapeutic agent (docetaxel),[10,11] and the systemically-administered immunotherapy agent pembrolizumab (Keytruda®) that was approved for BCG-unresponsive CIS disease in January 2020.[12]

Current therapies for BCG-unresponsive NMIBC are not successful in many patients, supporting the need for new bladder-preserving treatments.[11] Two such new intravesical therapies are reviewed in this report:

- **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.[13,14] 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 anti-epithelial cell adhesion molecule (EpCAM) single-chain antibody linked to *Pseudomonas* exotoxin A that binds to the cancer cell and then releases the toxin into the cell, inducing cell death.[15] 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.

Insights Gained from Discussions with Patients and Patient Groups

Discussions with individual patients and patient advocacy groups identified important insights. Common themes included the need for better therapeutic options, the demands of current treatment, the possible tradeoff between deciding to avoid removal of the bladder (cystectomy) with risking cancer progression, and the impact of bladder cancer on quality of life regardless of whether they keep their bladder or have it removed.

A wide range of deficiencies with currently available treatments for bladder cancer were noted.

- Though some patients derive benefit from existing therapies, many have high-risk NMIBC that does not respond, or patients have side effects requiring stopping therapy.
- Even for those whose cancers respond, there is a need for ongoing treatment, and that treatment can subsequently fail for a variety of reasons.
- The net result is that for many patients with NMIBC that is unresponsive to BCG, there are limited treatment options available that are bladder preserving.

The profound impact of bladder cancer on the lives of patients with NMIBC and their families and caregivers were emphasized.

- Side effects of current instillation therapies include burning, sense of urinary urgency, and discomfort in the groin/pelvis.
- Over time, these side effects can become more severe, and can lead to switching to other instillation therapies that can have similar side effects.
- For those responding to instillation therapies, maintenance therapy is needed and is burdensome in that it requires regular visits and monitoring between courses of therapy.
- The rigors of treatment and the uncertainty associated with managing bladder cancer over time all place a large burden on patients and their families and caregivers.

The toll on patients with bladder cancer includes important economic consequences.

- Bladder cancer is one of the costliest cancers to treat.
- Even with insurance coverage, there is a financial burden on patients, including the time and costs involved in travel to treatments and monitoring.
- For those still working, bladder cancer can result in disability or lost productivity and wages.

Patients with BCG-unresponsive NMIBC also face the burden of deciding whether to undergo cystectomy.

- By selecting bladder-preserving treatments and delaying cystectomy, which is likely to be curative in those with only localized cancer, it is possible that progression to metastatic disease may occur and there is no longer a curative option for the patient.
- The tradeoff between the permanent loss of their bladder with the potential risk of disease progression or even death due to bladder cancer can be very stressful.

Even for those in whom cystectomy is an option, no one wants to have their bladder removed.

- The impact of cystectomy is large, not only for maintaining the ability to normally void, but cystectomy can have a large negative impact on sexual function.
- For those considering cystectomy, most will have a urinary diversion where the urine drains through an opening in the side of the abdomen into a bag.
- There is the possibility of creating an artificial bladder from a section of the bowel, but one patient described it as a treatment “not for the faint of heart.”

Comparative Clinical Effectiveness

We evaluated the comparative clinical effectiveness of nadofaragene firadenovec and oportuzumab monatox in adults with BCG-unresponsive, high risk NMIBC. This includes patients with biopsy findings showing CIS ± Ta/T1 (population 1) or non-CIS with high grade (HG) Ta/T1 (population 2). Unresponsive populations include both patients whose cancers did not respond to a reasonable course of treatment with BCG or other chemotherapeutics and patients whose cancers recurred after treatment within a short period of time (6-12 months).[16] We compared the therapies to each other, to gemcitabine with or without (±) docetaxel, and, in population 1, systemic pembrolizumab.

Our literature search identified 960 potentially relevant references (see Appendix Figure A1), of which 30 references met our inclusion criteria. Primary reasons for study exclusion included study populations outside our scope, reporting of outcomes not relevant to this review, and conference abstracts or posters reporting data subsequently published in peer-reviewed literature.

Of the 30 references, four references represented three trials of nadofaragene firadenovec. Five references represented three trials of oportuzumab monatox. Five references represented one trial of systemic pembrolizumab. Eleven references represented 11 studies of gemcitabine alone and five references represented five studies of gemcitabine in combination with docetaxel. One conference abstract of a study of gemcitabine in combination with docetaxel met eligibility criteria for inclusion, but there was insufficient information to categorize outcomes in a similar manner to the other therapies at the time of the report.[17]

All identified studies for nadofaragene firadenovec, oportuzumab monatox, and pembrolizumab were single arm, open-label prospective studies, and none compared the interventions to each other or another comparator. The pivotal trials of nadofaragene firadenovec and oportuzumab monatox included similar distributions of patients with CIS ±Ta/T1 and non-CIS with HG Ta/T1 and used the same definitions of BCG-unresponsive disease. However, the nadofaragene firadenovec Phase III trial required a biopsy at the 12-month evaluation, whereas the oportuzumab monatox Phase III trial did not. This biopsy could have resulted in additional patients being identified as having recurrent disease who would not have been found without biopsy. Efficacy outcomes were reported for all eligible patients in the nadofaragene firadenovec trial who received study drug, whereas patients who did not complete induction therapy were excluded in the oportuzumab monatox trial. At the time of this report, only data from the CIS ± Ta/T1 cohort of the pivotal trial of pembrolizumab was available. This trial included the additional inclusion criteria that patients either be ineligible for or decline cystectomy.

Table ES1. Pivotal Trials of Nadofaragene Firadenovec, Oportuzumab Monatox, and Pembrolizumab

Trials	Dose(s) Evaluated	Inclusion Criteria	Outcomes	Baseline Characteristics
NCT02773849 **Phase III open-label single arm (n=157)**	Intravesical rAd-IFNα/Syn3 $3x10^{11}$ vp/mL every 3 months up to 4 instillations	BCG-unresponsive NMIBC with CIS ± HG Ta/T1 or HG Ta/T1 only; At least 2 prior courses of BCG within a 12-month period	Primary: • CR in CIS ± HG Ta/T1 Secondary: • Durability of CR in patients with CIS ± HG Ta/T1 • Rate and durability of HG-RFS in patients with HG Ta/T1 disease	Safety population: • 107 (68%) CIS ± HG Ta/T1 • 50 (32%) HG Ta/T1 only • Median age (IQR): 71 years (66-77) • 129 (82%) Male • 151 (96%) had 2+ BCG courses
VISTA NCT02449239 Phase III open-label single arm (n=133)	30 mg intravesical oportuzumab monatox 2x/week for 6 weeks, then weekly for 6 weeks, then 2x/month for up to 24 months	BCG refractory or relapsing NMIBC with either CIS ± Ta/T1 or any grade Ta/T1 only; At least 2 prior courses of BCG	Primary: • CR and durability of CR in CIS ± HG Ta/T1 Secondary: • Rate and durability of HG-RFS in patients with HG Ta/T1 disease only	Safety population: • 93 (70%) CIS ± HG Ta/T1 • 40 (30%) HG Ta/T1 only • Mean age (SD): 73.5 years (8.8) • 103 (77%) Male • 133 (100%) 2+ BCG courses
KEYNOTE 057 NCT02625961 **Phase II, Single-Arm, Open-Label, Multi-Center (n=96)**	Pembrolizumab 200 mg IV every Q3W up to 24 months	BCG unresponsive NMIBC with CIS ± HG Ta/T1 and declined or ineligible for cystectomy	Primary: • CR Secondary: • Duration of response	• 100% CIS ± HG Ta/T1 • Median age (IQR): 73 years (44-92) • 81 (84.4%) Male • Median instillations, n (range): 12 (7-45)

CIS: carcinoma in situ, CR: complete response, HG: high grade, IQR: interquartile range, n: number, NMIBC: non-muscle invasive bladder cancer

We identified 11 trials of gemcitabine, of which eight were single-arm prospective trials, two were RCTs comparing gemcitabine to another agent, and one was a retrospective chart review. The trials varied in terms of eligibility criteria, baseline characteristics, treatment doses and schedules, and outcomes measured, and the majority were not-US based. Notably, outcomes stratified by tumor grade (CIS vs. Ta/T1) were generally not available. Two prospective trials included a sufficient mix of CIS (60% or greater) and Ta/T1 only patients (Table ES2).

Table ES2. Selected Trials of Gemcitabine

Trials	Dose(s) Evaluated	Inclusion Criteria	Outcomes	Baseline Characteristics
Dalbagni 2006 N=30 Phase II single arm	2,000 mg 2x/week intravesical gemcitabine for 3 weeks	CIS ± HG Ta/T1 or HG Ta/T1 only NMIBC refractory to BCG	• Complete response • Recurrence free survival	• 23 (77%) CIS ± HG Ta/T1 • 7 (20%) HG Ta/T1 only • Median age: 70 years • 22 (73%) Male
Skinner 2013 N=47 Phase II single arm	2,000 mg intravesical gemcitabine 1x/week for 6 weeks then monthly up to 40 weeks	BCG unresponsive (relapse or refractory to at least 2 courses of BCG) NMIBC with CIS ± HG Ta/T1, HG or low grade (LG) Ta/T1	• Complete response • Recurrence free survival	• 28 (60%) CIS ± HG Ta/T1 • 14 (30%) HG Ta/T1 only • 5 (10%) LG Ta/T1 only • Mean age (SD): 69.3 years (5.4) • 13 (65%) Male

CIS: carcinoma in situ, HG: high grade, LG: low grade, N: total number, NMIBC: non-muscle invasive bladder cancer, SD: standard deviation

We identified four US-based retrospective studies of sequential gemcitabine and docetaxel, of which one provided sufficient data on the CIS population.[18] One conference abstract of a prospective study of gemcitabine and docetaxel did not have sufficient data at the time of the report to be reported.

Table ES3. Selected Retrospective Study of Sequential Gemcitabine and Docetaxel

Study	Dose Evaluated	Inclusion Criteria	Outcomes	Baseline Characteristics
Steinberg 2020 N=276 Retrospective chart review	1,000 mg intravesical gemcitabine followed by 37.5 mg docetaxel 1x/week for 6 weeks	BCG unresponsive NMIBC with CIS ± Ta/T1 HG or HG Ta/T1 only	Primary: • Recurrence free survival Secondary: • High-grade recurrence free survival • Progression	173 (62.7%) CIS ± HG Ta/T1; 72 (26%) HG Ta/T1; 31 (11%) LG Ta/T1 Median age: 73 years 224 (81.1%) Male BCG courses: 128 (46.4%) 2+

CIS: carcinoma in situ, HG: high grade, LG: low grade, N: total number, NMIBC: non-muscle invasive bladder cancer

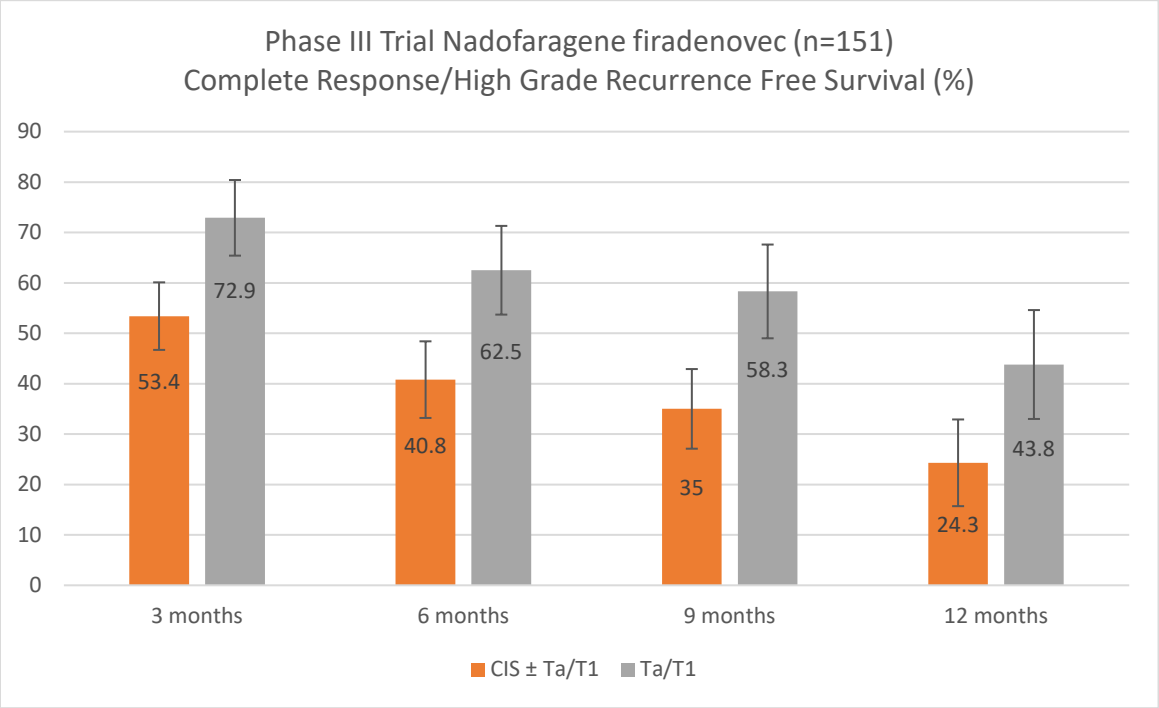
Clinical Benefits

Complete Response and High-Grade Recurrence Free Survival

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. Overall, CR/HGRFS was higher for the Ta/T1 population and declined over time (see Figures ES1-ES3).

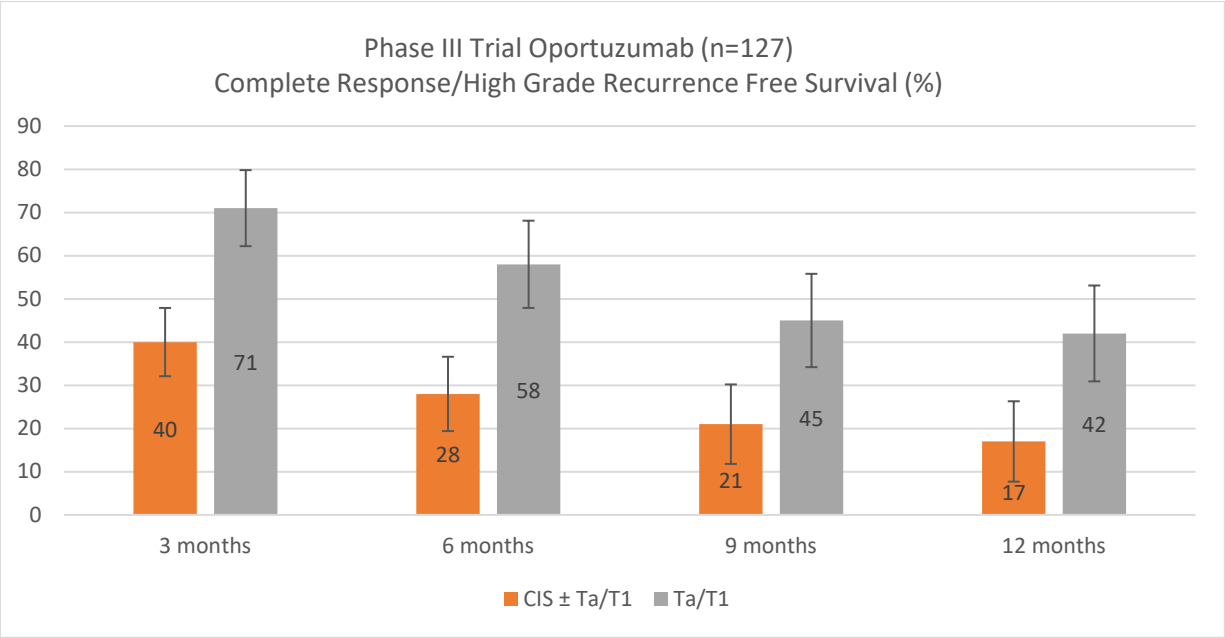
Nadofaragene firadenovec: In the Phase III trial, fifty-five (53.4%) of 103 patients with CIS ± HG Ta/T1 achieved a CR at three months, compared to 35 (72.9%) of 48 patients with HG Ta/T1 disease alone. For the CIS ± Ta/T1 group, HGRFS was 40.8%, 35.0%, and 24.3% at six, nine, and 12 months. For the HG Ta/T1 group, HGRFS was 62.5%, 58.3%, and 43.8% for the same time periods (Figure ES1). The median duration of response in the nadofaragene firadenovec Phase III trial was 9.69 months in the CIS population and 12.35 months in the Ta/T1 population. In the CIS ± Ta/T1 group, 5 (4.9%) of 103 patients progressed to MIBC, while 3 (6.3%) of the 48 patients in the HG Ta/T1 only group progressed. The rate of cystectomy was 26% at 12 months in the overall study population.[19]

Figure ES1. Phase III Results of Nadofaragene Firadenovec: Complete Response and High-Grade Recurrence Free Survival, CIS ± Ta/T1 and Ta/T1



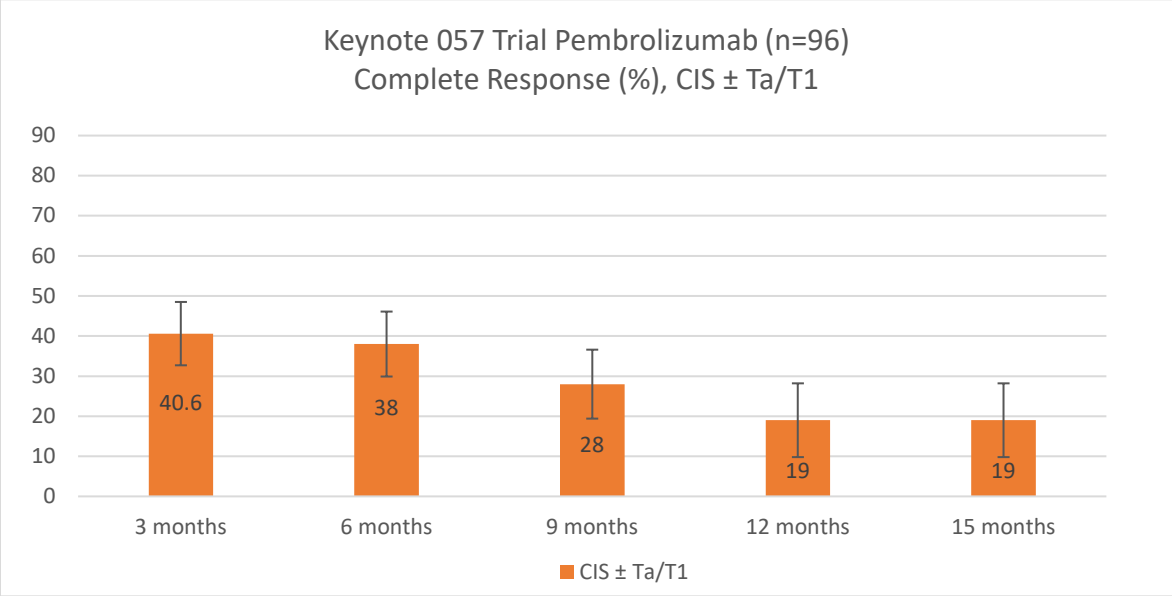
Oportuzumab monatox: In the Phase III VISTA trial, CR in the CIS ± Ta/T1 group was 40%, 28%, 21%, 17% at three, six, nine, and 12 months. For the HG Ta/T1 group, HGRFS was 71%, 58%, 45%, and 42% at three, six, nine, and 12 months (Figure ES2). The median duration of response in the oportuzumab monatox Phase III trial was 9.4 months in the CIS population and 13.2 months in the Ta/T1 population. Kaplan-Meier estimated progression to MIBC was 4% and cystectomy rates were 26% at 12 months in the overall study population.[20]

Figure ES2. Phase III Results of Oportuzumab Monatox: Complete Response and High-Grade Recurrence Free Survival, CIS ± Ta/T1 and Ta/T1



Pembrolizumab: In the Phase II Keynote-057 trial, 39 (40.6%) of 96 patients with CIS disease had a CR at three months (95% CI: 30.7 to 51.1). Based on a Kaplan-Meier curve for duration of CR, CR rates were 38%, 28%, 19% and 19% at six, nine, 12, and 15 months, respectively (Figure ES3). The median duration of response was 16.2 months (range 0-30.4 months).[21]

Figure ES3. Phase II Results of Pembrolizumab: Complete Response, CIS ± Ta/T1



Gemcitabine ± Docetaxel: In the mixed CIS and Ta/T1 study populations for two Phase II studies of gemcitabine, recurrence free survival (of any type) at 12 months was 21-28% and median duration of response was 3.6-6.1 months.[22,23] In the retrospective study of sequential gemcitabine and docetaxel, HGRFS at 12 months was 60% in the CIS population and 69% in the HG Ta/T1 population.[18]

Harms

Harms assessed in the single-arm trials included treatment-emergent adverse events (TEAEs), treatment-related adverse events (TRAEs), grade 3-5 TEAEs, serious TEAEs, and discontinuation due to a TEAE.

Nadofaragene firadenovec: In the Phase III trial, 157 patients were evaluated for safety of nadofaragene firadenovec. One hundred forty-six (93%) reported any TEAE, of which 29 (18%) were grade 3-5 and 14 (9%) were serious (Table ES4). The most commonly reported drug-related AE was irritative voiding symptoms. Serious treatment-related events included one case each of syncope, sepsis, and hematuria.[19,24,25]

Oportuzumab monatox: As of the 12-month data output (05/29/2019 data cut-off) for the Phase III trial, 117 patients (88%) of 133 included in the safety population reported any TEAE (Table ES4). 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 (<1%) was reported.[26]

Pembrolizumab: One hundred two patients were evaluated in the safety population of the Phase II Keynote-057 trial (Table ES4). 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 and 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.

Table ES4. Adverse Events in Phase III Trials of Nadofaragene Firadenovec (n=157) and Oportuzumab Monatox (n=133) and Phase II Trial of Pembrolizumab (n=102)

Adverse Events	Nadofaragene n (%)	Oportuzumab n (%)	Pembrolizumab n (%)
Treatment-Emergent AE	146 (93)	117 (88)	99 (97.1)*
Treatment-Related AE	110 (70.1)	66 (50)	67 (65.7)
Grade 3-5 TEAE	29 (18)	28 (21)	30 (29.4)*
Serious TEAE	14 (9)	19 (14)	26 (25.5)*
Death	6 (3.8)	1 (<1)	2 (2.0)
Discontinuation due to TEAE	3 (1.9)	4 (3.0)	10 (9.8)*
Discontinuation due to Serious AE	NR	3 (2.3)	NR

AE: adverse event, n: number, NR: not reported

*Any adverse event

Gemcitabine ± Docetaxel: Harms of gemcitabine with and without docetaxel were not reported consistently and estimates varied. The most commonly 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%.

Uncertainties and Controversies

For patients with BCG-unresponsive NMIBC, nadofaragene firadenovec and oportuzumab monatox were evaluated in single-arm trials without 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.

In terms of study populations, patient eligibility includes several pathological findings that can lead to differences among trials. One must select studies with similar overall proportions of patients with these pathological findings or look for studies that report outcomes in comparable subgroups.

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.

As with differences among trials in terms of study population characteristics, the nature of the outcome assessed and differences in censoring of patients 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.

Nadofaragene firadenovec and oportuzumab monatox appear to have few serious side effects and given their administration directly into the bladder, may be safer than pembrolizumab that is given systemically. Nevertheless, as new therapies, potential side effects of nadofaragene firadenovec and oportuzumab monatox will require longer term evaluation in more patients.

Guidelines recommend that for patients with BCG-unresponsive NMIBC, physicians discuss that radical cystectomy is the gold standard treatment. Trying additional bladder-preserving treatments for those who could undergo a potentially curative cystectomy may result in a loss of cure if the cancer progresses.

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. Since most patients receiving nadofaragene firadenovec or oportuzumab monatox progress or recur over time, it is possible that by delaying potentially curative cystectomy these treatments may lead more patients to develop metastatic disease or die from bladder cancer.

A number of chemotherapeutic drugs, such as gemcitabine ± docetaxel, instilled into the bladder have been examined for patients with BCG-unresponsive NMIBC. Despite differences in patient populations and study design making any direct comparisons exceedingly difficult, similar outcomes and expected lower costs suggest that trials comparing these older chemotherapeutic drugs with newer agents are warranted.

Summary and Comment

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. Few serious harms were reported and there were low discontinuation rates. Nadofaragene firadenovec is given much less frequently than oportuzumab monatox.

The single-arm trials limit the ability to compare nadofaragene firadenovec and oportuzumab monatox to each other and to the comparators. The lack of a placebo or active comparator, though meeting FDA guidance, results in uncertainty about the magnitude of benefit of these new agents. In addition, varied patient populations and histologies, differences in prior treatments, short-term outcomes reported in a relatively small number of individuals, and lack of long-term follow-up limit the ability to reach conclusions about the therapies in comparison with best supportive care, and preclude reaching conclusions comparing the therapies with each other or with the comparator therapies. Finally, since most patients treated with nadofaragene firadenovec and oportuzumab monatox will end up having progression or recurrence over time, it remains to be seen whether delaying potentially curative therapy with cystectomy leads to greater long-term disease related mortality. The magnitude of any such increase in mortality would be key to assessing the balance between benefits and harms.

As such, we have rated both nadofaragene firadenovec and oportuzumab monatox as "comparable or incremental" ("C++") when compared with best supportive care. 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. Given the large uncertainties about comparative benefits and harms, we have rated comparisons between the interventions with each other and with the comparators of pembrolizumab and gemcitabine ± docetaxel as "insufficient" ("I"). These ratings are shown in Table ES5.

Table ES5. Summary of Evidence Ratings for Nadofaragene Firadenovec and Oportuzumab Monatox

Intervention	Tumor Grade	ICER Evidence Rating
Nadofaragene Firadenovec vs. best supportive care	Overall	C++
Oportuzumab Monatox vs. best supportive care	Overall	C++
Nadofaragene Firadenovec vs. Oportuzumab Monatox	Overall	I
Nadofaragene Firadenovec vs. Pembrolizumab	CIS ± HG Ta/T1	I
Oportuzumab Monatox vs. Pembrolizumab	CIS ± HG Ta/T1	I
Nadofaragene Firadenovec 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)

Long-Term Cost Effectiveness

The primary aim of the analysis was to evaluate the cost effectiveness of nadofaragene firadenovec and oportuzumab monatox compared with no bladder cancer treatment in BCG-unresponsive NMIBC. Although our initial intent was to include pembrolizumab and gemcitabine ± docetaxel as comparators, given the "I" evidence ratings, direct comparisons between therapies were not made. All treatments, including pembrolizumab and gemcitabine ± docetaxel, were compared with a hypothetical treatment whose effectiveness at achieving complete response (CR) at 3 months could be varied in sensitivity analyses. The comparator hypothetical treatment's effectiveness was set to a CR of 0% at three months in the base case.

The population of interest for this economic evaluation was the prevalent cohort of individuals in the US with BCG-unresponsive high-risk NMIBC. Two separate subgroups of patients were evaluated: Population 1 were patients who had CIS ± Ta/T1; and population 2 were those with high grade (HG) Ta/T1 disease.

We developed a *de novo* semi-Markov model with time-varying proportions of patients with high-grade recurrence-free survival (HGRFS) and mortality. The model was primarily informed by key clinical trials, prior relevant economic models, systematic literature reviews, and input from diverse stakeholders (patients, advocacy groups, clinicians, payers, researchers, and manufacturers of these

agents). The base case used a US health care sector perspective. Costs and outcomes were discounted at 3% annually. The model cycle was three months, based on assessment of treatment response, typical follow-up, and prior models.

Simulated patients entered the model in Initial Treatment and received treatment with nadofaragene firadenovec, oportuzumab monatox, pembrolizumab, gemcitabine ± docetaxel, or the comparator hypothetical treatment. Patients who had a CR to therapy transitioned from "Initial Treatment" to "Disease-free" at the end of the first cycle. Those without a CR at three months moved to "Persistent/Recurrent NMIBC." As the model progressed, patients could move to "Persistent/Recurrent NMIBC," "MIBC," "Post-cystectomy," "Metastatic Disease," or "Death" according to probabilities derived from clinical trials, epidemiological studies of NMIBC and related conditions, and age- and gender-adjusted mortality tables. Utility and cost information was abstracted from published literature and applied to Markov states in the model according to the definitions of the Markov states.

Key Assumptions

The model required several assumptions, which are described in Table ES6.

Table ES6. Key Assumptions

Assumption	Rationale
Patients who are disease-free or who have metastatic disease will not have a cystectomy.	Data are not available describing the probability that patients who are disease-free or who have metastatic disease elect to undergo cystectomy. Patients who are disease-free do not require cystectomy unless there is disease progression. Patients with metastatic disease will require systemic rather than local therapy.
States of persistent or recurrent NMIBC have similar utilities and costs.	We have not identified data documenting differences in utility or costs between persistent and recurrent NMIBC.
Patients with no treatment have disease progression at the same (average) rate as those from longer-term studies in whom treatment is not effective.	We identified no data informing disease progression in patients who receive no bladder cancer treatment. Most data available are from single-arm studies with active treatment. This assumption is necessary to compare the new treatments to no bladder cancer treatment.
Patients who have a complete response to treatment do not develop MIBC within a 3-month period. Instead they progress to NMIBC, and then to MIBC, over a period longer than the model cycle length.	This assumption makes estimating other probabilities easier in the model, given the limited availability of detailed data on NMIBC progression. The assumption is supported by clinical trials for nadofaragene firadenovec, oportuzumab monatox, and pembrolizumab, in which 100% of patients showed progression-free survival at 3 months.
Patients who have complete response or persistent/recurrent NMIBC do not progress to metastatic disease directly within a 3-month period. Instead, they progress through NMIBC (for those with complete response) and MIBC to metastatic disease.	This assumption makes estimating other probabilities easier in the model, given the limited availability of detailed data on progression to metastatic disease. The assumption is supported by several studies.

Model Inputs

For population 1, the probability of moving from "Disease-free" to "Persistent/Recurrent NMIBC" was determined from CR, when available, at 6, 9, and 12 months and were time varying. When CR was not reported, as in the case of gemcitabine ± docetaxel, HGRFS was used as a proxy for CR. For population 2, the probability of moving from "Disease-free" to "Persistent/Recurrent NMIBC" was determined from HGRFS survival at 6, 9, and 12 months and were time varying. The probability of HGRFS between 12 and 24 months was used to estimate the probability of remaining in the "Persistent/Recurrent NMIBC" Markov state for all time periods greater than 12 months. Progression-free survival was used to estimate transitions from "Persistent/Recurrent NMIBC" to "MIBC." Since these estimates were not available for gemcitabine ± docetaxel or the hypothetical treatment comparator, the highest transition probability value from those calculated for nadofaragene firadenovec and oportuzumab monatox was used (i.e., 1.4% for population 1 and 3.0% for population 2). For all other model transitions, data were collected from other longer-term epidemiologic studies and clinical trials.

Since 12-month assessments of CR and HGRFS for nadofaragene firadenovec included biopsy, and those for oportuzumab monatox did not, we conducted scenario analyses to estimate the impact of using a biopsy to determine the proportion of patients classified as having recurrence. We also varied the effectiveness of the hypothetical treatment from a CR of 0% to 40% in population 1 and a HGRFS of 0% to 60% in population 2. These results were presented alongside the base case results.

Health state utilities for "Initial Treatment," "Disease Free," "Persistent/Recurrent NMIBC," and "MIBC" were obtained from a single study evaluating the EQ-5D in 472 patients with NMIBC.[27] The utility for "Metastatic Disease" was obtained from a study of 270 patients enrolled in the KEYNOTE-045 trial with metastatic urothelial carcinoma.[28] The "Post-Cystectomy" utility value was obtained from a decision model report where utility was estimated from 25 urologists using the standard gamble method.[29]

Drug utilization and treatment duration, obtained from clinical trials, were used to determine total treatment costs for nadofaragene firadenovec, oportuzumab monatox, pembrolizumab, and gemcitabine ± docetaxel. Since the prices for nadofaragene firadenovec and oportuzumab monatox were not available at the time of this report, the price for nadofaragene firadenovec was set to the annual price of pembrolizumab. The price of oportuzumab monatox was set at $150,000 per year, an estimated price net of rebates that was communicated by Sesen Bio. The price for pembrolizumab was derived using the US Department of Veteran Affairs Office of Procurement Federal Supply Schedule (FSS) prices.[30] The price for gemcitabine ± docetaxel was estimated using WAC, obtained from Micromedex Red Book.[31] Drug cost inputs are shown in Table ES7.

Table ES7. Drug Cost Inputs

Intervention	Administration	Unit	WAC or FSS per Unit	Net Price per Dose	Annual Drug Cost‡
Nadofaragene Firadenovec	$3x10^{11}$ vp/mL (75 mL), administered by intravesical instillation every 3 months (total of 4 doses per year)	$3x10^{11}$ vp/mL (75 mL)	$41,084**	$41,084**	$164,337**
Oportuzumab Monatox	30 mg administered by intravesical instillation twice weekly for first 6 weeks, then once weekly for 6 weeks, then every other week thereafter (total of 36 doses in first year)	30 mg	$4,167**	$4,167**	$150,000***
Pembrolizumab	200 mg IV over 30 minutes every 3 weeks or 400 mg IV over 30 minutes every 6 weeks for up to 24 months (total of 17.4 doses per year)	200 mg	$9,455*	$9,455*	$164,337
Gemcitabine ± Docetaxel	Gemcitabine 1000 mg and docetaxel 37.5 mg administered weekly for 6 weeks by intravesical instillation	1000 mg and 160 mg	$36.90 and $153.00	$36.90 and $35.86	$437#

FSS: Federal Supply Schedule, WAC: wholesale acquisition cost

*FSS as of August 26, 2020

**The estimated price for nadofaragene firadenovec was assumed to be the annual price of pembrolizumab.

***The estimated price for oportuzumab monatox was provided through communication with Sesen Bio.

‡The annual drug cost includes drug acquisition cost for a full 365 days.

#The annual drug cost for gemcitabine ± docetaxel was estimated for the 6-week course of therapy only.

The model estimated total discounted lifetime costs, QALYs, evLYGs, life years gained, and time in progression-free health state, as well as cost/QALY, cost/evLYG, cost per life year, and cost per year in progression-free state.

Base-Case Results

The cost per QALY gained, cost per evLYG, and cost per year in a progression-free state for nadofaragene firadenovec, oportuzumab monatox, pembrolizumab, and gemcitabine ± docetaxel compared with the hypothetical treatment (with the complete response probability set to 0%), are shown in Table ES8 (for the CIS ± Ta/T1 subgroup) and Table ES9 (for the HG Ta/T1 subgroup). Both nadofaragene firadenovec and oportuzumab monatox have incremental cost-effectiveness ratios above $150,00 for the CIS ± Ta/T1 subgroup and less than $150,00 for the HG Ta/T1 subgroup.

Table ES8. Incremental Cost-Effectiveness Ratios for Nadofaragene Firadenovec, Oportuzumab Monatox, Pembrolizumab, and Gemcitabine ± Docetaxel Compared to the Hypothetical Treatment Comparator 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 based on annual price of pembrolizumab

Table ES9. Incremental Cost-Effectiveness Ratios for Nadofaragene Firadenovec, Oportuzumab Monatox and Gemcitabine ± Docetaxel Compared to the Hypothetical Treatment Comparator 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 based on annual price of pembrolizumab

Since 12-month assessments of CR and HGRFS for nadofaragene firadenovec included a biopsy, and those for oportuzumab monatox did not, we evaluated the impact of determining the 1) inclusion and 2) exclusion of patients with recurrence of their bladder cancer assessed via biopsy alone for both nadofaragene firadenovec and oportuzumab monatox. It should be noted that for nadofaragene firadenovec, the reported numbers and proportions of patients with CR and HGRFS at 12 months were reported, including a description of patients who were diagnosed with biopsy alone for each group (as a note). Since biopsy was not conducted at 12 months for oportuzumab

monatox, the number of patients who had recurrence diagnosed with biopsy alone were not known. We therefore imputed the number of patients who might have had recurrence diagnosed via biopsy alone at 12 months (i.e., three patients in population 1 and two patients in population 2). Accounting for differences in 12-month assessments improved the incremental cost-effectiveness ratios of nadofaragene firadenovec compared to oportuzumab monatox (see tables ES10 and ES11).

Table ES10. Scenario Analysis of the Incremental Cost-Effectiveness Ratios for Nadofaragene Firadenovec and Oportuzumab Monatox in Patients with CIS ± Ta/T1 Alone Accounting for Recurrence Being Assessed via Biopsy Alone

Treatment	Comparator	Base Case	Inclusion of Patients Assessed via Biopsy	Exclusion of Patients Assessed via Biopsy
Nadofaragene Firadenovec*	Hypothetical Treatment	$151,000	$151,000	$142,000
Oportuzumab Monatox	Hypothetical Treatment	$382,000	$435,000	$382,000

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

Table ES11. Scenario Analysis of the Incremental Cost-Effectiveness Ratios for Nadofaragene Firadenovec and Oportuzumab Monatox in Patients with High Grade Ta/T1 Accounting for Recurrence Being Assessed via Biopsy Alone

Treatment	Comparator	Base Case	Inclusion of Patients Assessed via Biopsy	Exclusion of Patients Assessed via Biopsy
Nadofaragene Firadenovec*	Hypothetical Treatment	$93,000	$93,000	$86,000
Oportuzumab Monatox	Hypothetical Treatment	$123,000	$136,000	$123,000

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

In a sensitivity analysis, we varied the effectiveness of the hypothetical treatment from a CR of 0% to 40% in population 1 and a HGRFS of 0% to 60% in population 2. As the effectiveness of the hypothetical treatment increased, the incremental cost-effectiveness ratios of both nadofaragene firadenovec and oportuzumab monatox also increased (see Tables ES12 and ES13).

Table ES12. Impact of Varying the Effectiveness of the Hypothetical Treatment Comparator on the Incremental Cost-Effectiveness Ratios for Nadofaragene Firadenovec and Oportuzumab Monatox Compared to Hypothetical Treatment in Patients with CIS ± Ta/T1

Effectiveness of Hypothetical Treatment (% with Complete Response at 3 Months)	Nadofaragene Firadenovec* Cost per QALY Gained	Oportuzumab Monatox Cost per QALY Gained
0% (Base Case)	$151,000	$382,000
10%	$153,000	$394,000
20%	$155,000	$407,000
30%	$160,000	$444,000

QALY: quality-adjusted life year

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

Table ES13. Impact of Varying the Effectiveness of the Hypothetical Treatment Comparator on the Incremental Cost-Effectiveness Ratios for Nadofaragene Firadenovec and Oportuzumab Monatox Compared to Hypothetical Treatment in Patients with High Grade Ta/T1

Effectiveness of Hypothetical Treatment (% with Complete Response at 3 Months)	Nadofaragene Firadenovec* Cost per QALY Gained	Oportuzumab Monatox Cost per QALY Gained
0% (Base Case)	$93,000	$123,000
10%	$94,000	$125,000
20%	$98,000	$131,000
30%	$107,000	$147,000
40%	$125,000	$182,000
50%	$157,000	$257,000
60%	$225,000	$493,000

QALY: quality-adjusted life year

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

Sensitivity Analyses

To demonstrate effects of uncertainty on both costs and health outcomes, we varied input parameters using available measures of parameter uncertainty (i.e., standard errors) or reasonable ranges to evaluate changes in cost per additional QALY for nadofaragene firadenovec and oportuzumab monatox compared to the hypothetical treatment in both subgroups. The primary drivers of model uncertainty for population 1 (CIS) were the transition probabilities for 1) disease progression (i.e., moving from NMIBC to MIBC); 2) having recurrence, especially after 12 months (i.e., moving from Disease Free to NMIBC after 12 months); and 3) achieving CR (treatments and the hypothetical treatment). Although the base-case restricted direct movement from Disease Free to MIBC, when subjected to sensitivity analyses this transition probability was also an important contributor to the analysis results. Cost inputs had minimal impact on the cost-effectiveness results. The utility of being in the Disease-Free state also had some impact on the model results. Results were similar for patients in population 2 (HG Ta/T1), although the contributions of each variable differed slightly from population 1. The full one-way sensitivity analyses are shown in

Figures 5.2-5.5. Results of the probabilistic sensitivity analyses are shown in Tables ES14 and ES15. Results for nadofaragene firadenovec and oportuzumab monatox were generally above a cost-effectiveness threshold of $150,000 per QALY gained in the CIS ± Ta/T1 subgroup (43.1% and 11.9%, respectively) while those in the HG Ta/T1 subgroup were generally below $150,000 per QALY (58.5% and 67.2%, respectively).

Table ES14. Probabilistic Sensitivity Analysis Results: Nadofaragene Firadenovec and Oportuzumab Monatox Compared to Pembrolizumab and Hypothetical Treatment in Patients with CIS ± Ta/T1

	Cost Effective at $50,000 per QALY	Cost Effective at $100,000 per QALY	Cost Effective at $150,000 per QALY	Cost Effective at $200,000 per QALY	Cost Effective at $250,000 per QALY
Nadofaragene Firadenovec	0.2%	15.7%	44.8%	63%	74.3%
Oportuzumab Monatox	0%	1.5%	12.2%	22.2%	30.7%

QALY: quality-adjusted life year

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

Table ES15. Probabilistic Sensitivity Analysis Results: Nadofaragene Firadenovec and Oportuzumab Monatox Compared to Hypothetical Treatment in Patients with High Grade Ta/T1

	Cost Effective at $50,000 per QALY	Cost Effective at $100,000 per QALY	Cost Effective at $150,000 per QALY	Cost Effective at $200,000 per QALY	Cost Effective at $250,000 per QALY
Nadofaragene Firadenovec	8.3%	60.5%	82.1%	89.9%	93.8%
Oportuzumab Monatox	3.7%	41.2%	65.7%	78.8%	84.4%

QALY: quality-adjusted life year

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

Threshold Analyses

Tables ES16 and ES17 show the annual prices required to meet cost-effectiveness thresholds of $50,000, $100,000, and $150,000 per QALY gained using the base case inputs for all other variables except drug price.

Table ES16. Threshold Analysis Results in Patients with CIS ± Ta/T1

	WAC per Unit	Net Price per Unit	Annual Price to Achieve $50,000 per QALY	Annual Price to Achieve $100,000 per QALY	Annual Price to Achieve $150,000 per QALY
Nadofaragene Firadenovec	N/A	N/A	$64,500	$114,000	$163,500
Oportuzumab Monatox	N/A	N/A	$21,700	$41,000	$60,400

N/A: not available, WAC: wholesale acquisition cost

Table ES17. Threshold Analysis Results in Patients with High Grade Ta/T1

	WAC per Unit	Net Price per Unit	Annual Price to Achieve $50,000 per QALY	Annual Price to Achieve $100,000 per QALY	Annual Price to Achieve $150,000 per QALY
Nadofaragene Firadenovec	N/A	N/A	$99,400	$175,000	$250,700
Oportuzumab Monatox	N/A	N/A	$69,300	$124,900	$180,500

N/A: not available, WAC: wholesale acquisition cost

Summary and Comment

In our analysis evaluating the cost effectiveness of nadofaragene firadenovec and oportuzumab monatox compared to the hypothetical treatment in both subgroups, we identified several limitations in the data available. Clinical trials evaluating nadofaragene firadenovec and oportuzumab monatox, as well as pembrolizumab, did not include control groups, making comparisons of these agents to each other difficult. Study samples were relatively small for each of the studied populations and there were differences in how outcomes were assessed. Long-term outcomes from the clinical trials suffered from a high degree of censoring, resulting in highly unstable estimates of long-term effectiveness. There were limited data on health care costs for patients with NMIBC and the data that did exist were dated. Similarly, health utility estimates were not available for post-cystectomy patients and those with metastatic disease, and some estimates had poor face validity.

Since price data were not available for nadofaragene firadenovec and oportuzumab monatox, reliable estimates for their cost-effectiveness could not be estimated, although a threshold analysis revealed prices that could be used as a comparison when pricing is announced. However, given that there was no reliable comparator and that there was a high degree of uncertainty in certain critical model parameters, these estimates should be interpreted cautiously.

Potential Other Benefits and Contextual Considerations

Our reviews seek to provide information on potential other benefits offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that would not have been considered as part of the evidence on comparative clinical effectiveness. These elements are listed in the table below.

Potential Other Benefits

Table ES18. Potential Other Benefits

Other Benefits	Description
This intervention offers reduced complexity that will significantly improve patient outcomes.	Nadofaragene firadenovec and oportuzumab monatox are given by bladder instillation and with similar side effects to other therapies and would not be expected to change the complexity of care.
This intervention will reduce important health disparities across racial, ethnic, gender, socio-economic, or regional categories.	Not applicable.
This intervention will significantly reduce caregiver or broader family burden.	New therapies for NMIBC unresponsive to BCG may reduce caregiver and family burden if outcomes are improved for those in whom existing therapies do not effectively and safely control disease progression.
This intervention offers a novel mechanism of action or approach that will allow successful treatment of many patients for whom other available treatments have failed.	Both nadofaragene firadenovec and oportuzumab monatox represent new therapies that reflect translational research in which improved understanding of the mechanisms of disease and cell transfer technologies have led to new therapies.
This intervention will have a significant impact on improving return to work and/or overall productivity.	It is uncertain whether the availability of new treatments for NMIBC unresponsive to BCG may allow some patients to remain working or improve productivity at work.
Other important benefits or disadvantages that should have an important role in judgments of the value of this intervention.	Nadofaragene firadenovec is given as an instillation therapy much less frequently than oportuzumab monatox and other chemotherapies.

Contextual Considerations

Table ES19. Potential Contextual Considerations

Contextual Consideration	Description
This intervention is intended for the care of individuals with a condition of particularly high severity in terms of impact on length of life and/or quality of life.	For patients with NMIBC unresponsive to BCG, there is a need for new bladder-preserving treatments. Currently, guidelines recommend physicians discuss that radical cystectomy is the most effective available treatment.
This intervention is intended for the care of individuals with a condition that represents a particularly high lifetime burden of illness.	Though many patients initially respond to instillation therapy with BCG or chemotherapies, recurrence and progression is common. These individuals face the risk of muscle invasive and metastatic disease, and even death due to bladder cancer.
This intervention is the first to offer any improvement for patients with this condition.	The FDA permitted single-arm trials of nadofaragene firadenovec and oportuzumab monatox because randomizing patients to placebo or minimally effective therapies was not felt to be ethical, and the only alternative is radical cystectomy.
Compared to "the comparator", there is significant uncertainty about the long-term risk of serious side effects of this intervention.	The single-arm trials of nadofaragene firadenovec and oportuzumab demonstrated few serious harms and there were low discontinuation rates. Questions remain about the development of new side effects over time.
Compared to "the comparator", there is significant uncertainty about the magnitude or durability of the long-term benefits of this intervention.	For new medicines that have been evaluated in single-arm trials with most patients recurring or progressing over time, it is uncertain whether delaying or avoiding cystectomy could result in a loss of cure if the cancer progresses.
There are additional contextual considerations that should have an important role in judgments of the value of this intervention.	Nadofaragene firadenovec and oportuzumab monatox are instilled into the bladder and are intended to work locally. Pembrolizumab which is given systemically has the potential to cause serious complications but may have the added advantage of preventing spread beyond the bladder.

Health-Benefit Price Benchmarks

As there were discrepancies in the clinical trials of nadofaragene firadenovec and oportuzumab monatox in how recurrence was assessed at 12 months (biopsy was conducted in all patients for nadofaragene firadenovec but not for oportuzumab monatox), we calculated two different scenarios: 1) an optimistic scenario excluding the recurrences identified by biopsy alone at the 12-month CR and HGRFS outcomes in both nadofaragene firadenovec and oportuzumab monatox studies; and 2) a conservative scenario assuming the recurrences identified by biopsy alone at the 12-month CR and HGRFS outcomes did happen in both the nadofaragene firadenovec and oportuzumab monatox studies. We included both scenarios in calculating the health-benefit price benchmarks.

The ICER health benefit price benchmark (HBPB) is a price range suggesting the highest price a manufacturer should charge for a treatment, based on the amount of improvement in overall health patients receive from that treatment, when a higher price would cause disproportionately greater losses in health among other patients due to rising overall costs of health care and health insurance. In short, it is the top price range at which a health system can reward innovation and better health for patients without doing more harm than good.

The HBPB range for nadofaragene firadenovec across both scenarios and both populations range from $158,600 to $262,000 per year. The HBPB range for oportuzumab monatox ranges from $92,800 to $162,100 per year. Note that determining an appropriate and fair health-benefit based price for this heterogeneous group of patients is made even more difficult by not having evidence on potential comparators, and that our base case assumption of no benefit to comparator therapy means the estimates above should be considered as upper bounds on prices.

Potential Budget Impact

We used the cost-effectiveness model to estimate the potential total budgetary impact of treatment with nadofaragene firadenovec or oportuzumab monatox for adults 18 years and older with BCG-unresponsive/refractory, high risk NMIBC, graded as CIS ± Ta/T1 or non-CIS with HG Ta/T1. As these products are under FDA review and prices have not been announced by the manufacturers, we used assumed placeholder prices and the three population-weighted threshold prices (at $50,000, $100,000, and $150,000 per QALY) for nadofaragene firadenovec and oportuzumab monatox in our estimates of budget impact. Pembrolizumab was not included in this analysis because of its established presence in the market.

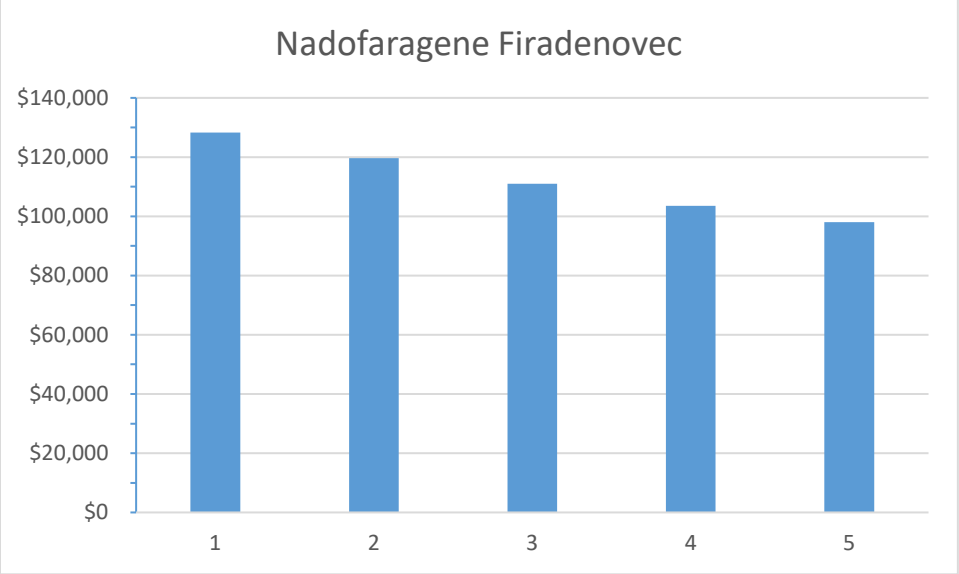
This potential budget impact analysis includes the estimated number of individuals in the US who would be eligible for these treatments. To estimate the size of the potential candidate population for treatment, we used the total number of adults 18 years and older with BCG-unresponsive/refractory, high risk NMIBC, graded as CIS ± Ta/T1 or non-CIS with HG Ta/T1.

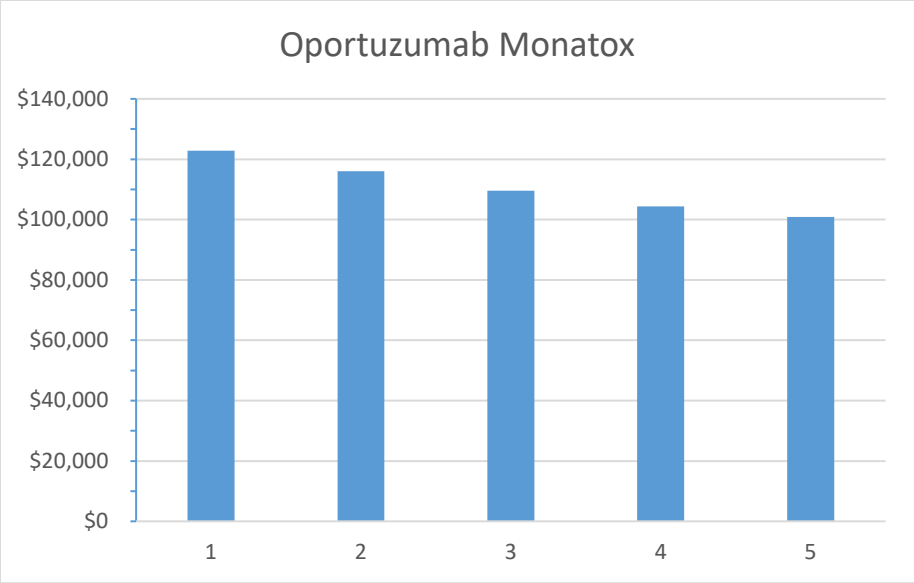
The National Cancer Institute's Surveillance, Epidemiology and End Results Program (SEER) estimates that prevalence of bladder cancer was 712,614 people in the US in 2017.[2] Kirkali et al. estimated that approximately 70% of bladder cancers present as NMIBC, with approximately 70% classified as Ta, 20% as T1, and 10% as CIS.[7] We assumed that T1 and CIS are considered high-grade disease while 10% of Ta cancers are considered high grade,[32] and that approximately 38% will be classified as BCG non-responders.[33] Applying these proportions to the estimated prevalent NMIBC population, we arrived at an estimate of 70,135 individuals as the eligible population for these treatments, with 73% (51,180) being Ta and T1 patients and 27% (18,956) being CIS patients. Among these eligible patients, we assumed a 20% uptake each year over five years, or 14,027 patients per year. We assumed that these patients would otherwise have been treated with "usual

care" as typified by the hypothetical treatment used in the base case (i.e., no specific bladder cancer-related treatment).

Figure ES4 illustrates the cumulative per-patient budget impact calculations for nadofaragene firadenovec and oportuzumab monatox compared to the "usual care" comparator, based on the assumed placeholder prices of $164,337 and $150,000 per one year of treatment, respectively. The average potential budgetary impact for nadofaragene firadenovec was an additional per-patient cost of approximately $128,000 in year one, with net annual savings in following years leading to cumulative costs per patient of approximately $98,000 by year five. The average potential budgetary impact for oportuzumab monatox followed a similar pattern, with an additional per-patient cost of approximately $123,000 in year one and net savings in following years leading to cumulative costs per patient of approximately $101,000 by year five.

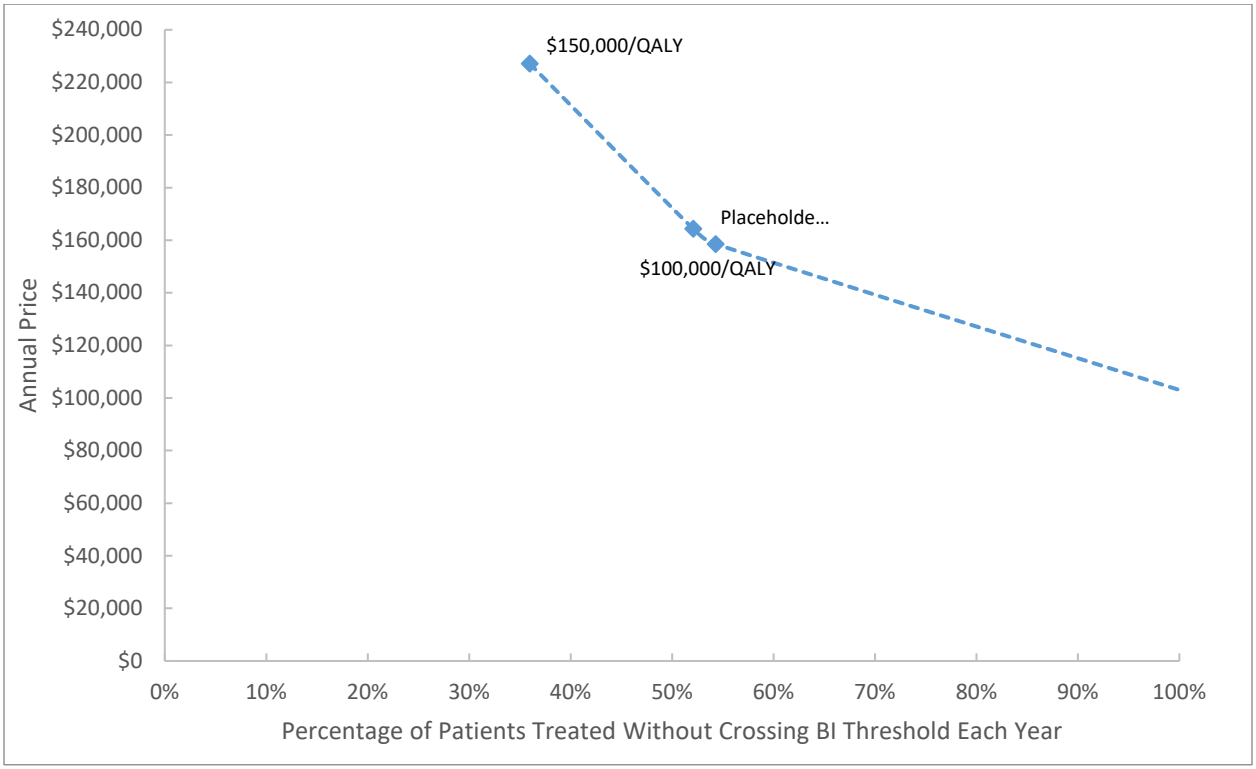
Figure ES4. Cumulative Net Cost Per Patient Treated with Nadofaragene Firadenovec and Oportuzumab Monatox at Assumed Placeholder Price Over a Five-Year Time Horizon





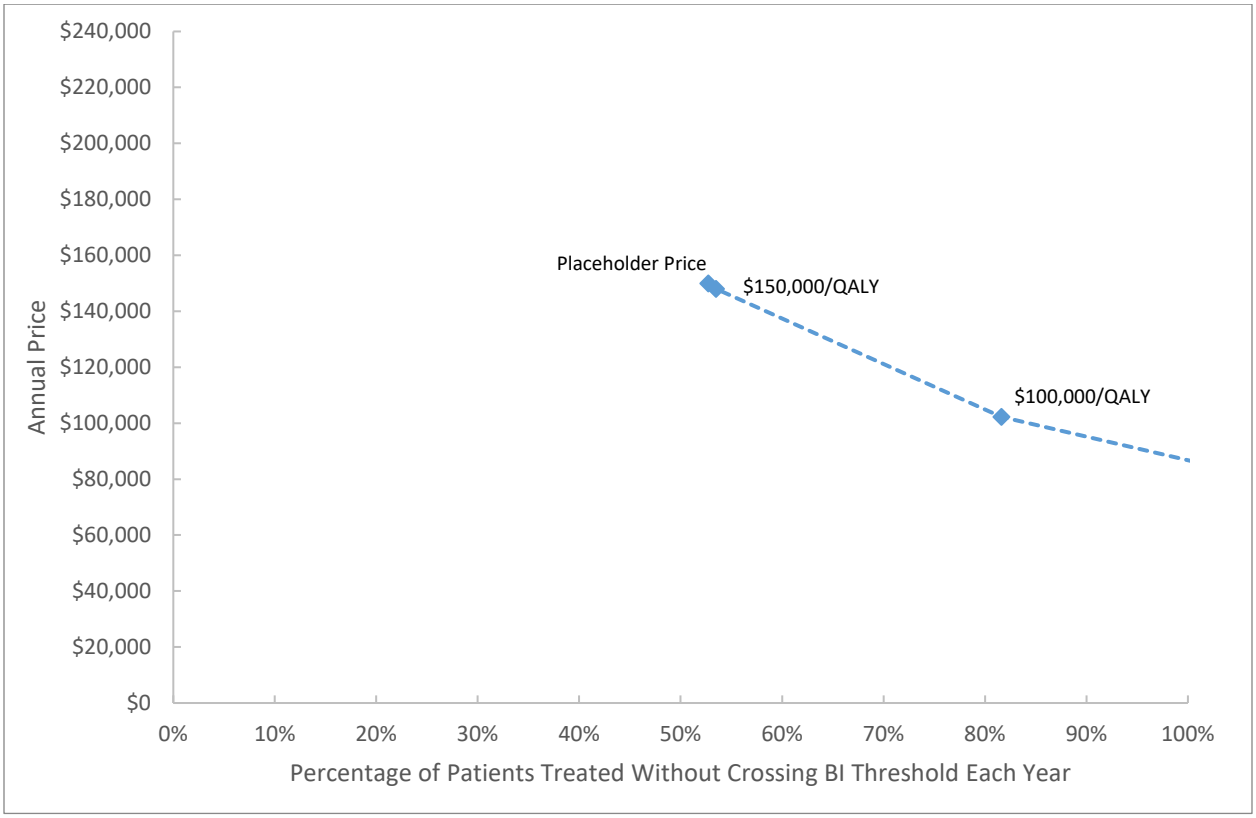
As shown in Figure ES5, approximately 52% of eligible patients could be treated with nadofaragene firadenovec in a given year without crossing the ICER budget impact threshold of $819 million at the assumed placeholder price. Approximately 36% and 54% of patients could be treated in a given year without crossing the budget impact threshold at the $150,000 and $100,000 per QALY threshold prices, respectively. All eligible patients could be treated at the $50,000 per QALY threshold price, reaching 90% of the potential budget impact threshold.

Figure ES5. Budgetary Impact of Nadofaragene Firadenovec in BCG-Unresponsive/Refractory, High Risk NMIBC Patients



As shown in Figure ES6, approximately 53% of eligible patients could be treated with oportuzumab monatox in a given year without crossing the ICER budget impact threshold of $819 million at the assumed placeholder price. Approximately 54% and 82% of patients could be treated in a given year without crossing the budget impact threshold at the $150,000 and $100,000 per QALY threshold prices, respectively. All eligible patients could be treated at the $50,000 per QALY threshold price, reaching 58% of the potential budget impact threshold.

Figure ES6. Budgetary Impact of Oportuzumab Monatox in BCG-Unresponsive/Refractory, High Risk NMIBC Patients



Midwest CEPAC Votes

The Midwest CEPAC Panel deliberated on key questions raised by ICER's report at a public meeting on November 20, 2020. The results of these votes are presented below, and additional information on the deliberation surrounding the votes can be found in the full report.

Patient population for questions 1-5: Adults with BCG-unresponsive, high-risk NMIBC (CIS ±Ta/T1 or non-CIS with high grade Ta/T1)

1. **Is the evidence adequate to demonstrate that the net health benefit of nadofaragene firadenovec is superior to that provided by best supportive care?**

Yes: 7 votes	No: 4 votes

The majority of the Council judged that the evidence was adequate to demonstrate that the net health benefit of nadofaragene firadenovec is superior to that provided by best supportive care, primarily because the Phase III trial showed reductions in recurrence and progression over time that exceeded the FDA threshold for effectiveness. Council members who voted "No" may have done so because of the lack of long-term data and

potential for losing the window of curability through cystectomy should nadofaragene firadenovec not prevent recurrence.

2. Is the evidence adequate to demonstrate that the net health benefit of oportuzumab monatox is superior to that provided by best supportive care?

Yes: 8 votes	No: 3 votes

The majority of the Council judged that the evidence was adequate to demonstrate that the net health benefit of oportuzumab monatox is superior to that of best supportive care, for similar reasons as were discussed for nadofaragene firadenovec.

3. Is the evidence adequate to distinguish the net health benefit of nadofaragene firadenovec from oportuzumab monatox?

Yes: 0 votes	***No: 11 votes***

The Council unanimously judged that the evidence was inadequate to demonstrate the net health benefit of nadofaragene firadenovec from oportuzumab monatox. The Council's vote was based on the lack of comparative data between nadofaragene firadenovec and oportuzumab monatox.

4. Is the evidence adequate to demonstrate that the net health benefit of nadofaragene firadenovec is superior to that provided by gemcitabine with or without docetaxel?

Yes: 0 votes	***No: 11 votes***

The Council unanimously judged that the evidence was inadequate to demonstrate that the net health benefit of nadofaragene firadenovec is superior to that provided by gemcitabine with or without docetaxel. Differences in the populations and outcomes assessed in the retrospective trials of gemcitabine with docetaxel precluded comparison with nadofaragene firadenovec.

Please note that this voting result does not match the meeting recording, because one Council member had entered their vote incorrectly through the voting software.

5. Is the evidence adequate to demonstrate that the net health benefit of oportuzumab monatox is superior to that provided by gemcitabine with or without docetaxel?

Yes: 0 votes	***No: 11 votes***

The Council unanimously voted that the evidence is not adequate to demonstrate that the net health benefit of oportuzumab monatox is superior to that provided by gemcitabine with or without docetaxel, for the reasons discussed above.

Patient population for questions 6-7: Adults with BCG-unresponsive, high-risk NMIBC due to CIS ±Ta/T1.

6. Is the evidence adequate to demonstrate that the net health benefit of nadofaragene firadenovec is superior to that provided by systemic pembrolizumab?

Yes: 0 votes	***No: 11 votes***

The Council unanimously judged that the evidence was inadequate to demonstrate that the net health benefit of nadofaragene firadenovec is superior to that provided by systematic pembrolizumab because the single-arm trials did not have a placebo group or active comparator, and had slight differences in study populations and how outcomes were assessed. In addition, the trial for nadofaragene firadenovec required a biopsy at 12 months, while the pembrolizumab trial did not.

7. **Is the evidence adequate to demonstrate that the net health benefit of oportuzumab monatox is superior to that provided by systemic pembrolizumab?**

Yes: 1 vote	***No: 10 votes***

The majority of the Council voted that the evidence was not adequate to demonstrate that the net health benefit of oportuzumab monatox is superior to that provided by systemic pembrolizumab, for similar issues as described above. However, at 12 months, the outcome assessments for oportuzumab and pembrolizumab were done similarly with cystoscopy and cytology, and neither required a biopsy. The CR rates at 12 months were identical for the two drugs.

For questions 8, 9 and 10: Please vote 1, 2, or 3 on the following potential other benefits and contextual considerations as they relate to nadofaragene firadenovec and oportuzumab monatox.

Question 8

1 (Suggests Lower Value)	2 (Intermediate)	3 (Suggests Higher Value)
This intervention will not differentially benefit a historically disadvantaged or underserved community		This intervention will differentially benefit a historically disadvantaged or underserved community
5 votes	***6 votes***	0 votes

All Council members voted either that the interventions will not differentially benefit a historically disadvantaged community, or that there will be an intermediate benefit.

Question 9

1 (Suggests Lower Value)	2 (Intermediate)	3 (Suggests Higher Value)
Small health loss without this treatment as measured by absolute QALY shortfall.		Substantial health loss without this treatment as measured by absolute QALY shortfall.
4 votes	***4 votes***	3 votes

The Council votes were split between a small, intermediate, and substantial health loss as measured by absolute QALY shortfall. The Council discussed how this condition primarily affects older individuals, who have a relatively quality-adjusted life expectancy.

Question 10

1 (Suggests Lower Value)	2 (Intermediate)	3 (Suggests Higher Value)
Small health loss without this treatment as measured by proportional QALY shortfall.		Substantial health loss without this treatment as measured by proportional QALY shortfall.
1 vote	***7 votes***	3 votes

The majority of Council members voted that there would be an intermediate health loss without treatment for patients in this population, as measured by proportional QALY shortfall. The Council voted based on the proportional quality-adjusted life expectancy that would be lost without any additional treatment, which is 54%.

11. Please vote 1, 2, or 3 on the following potential other benefits and contextual considerations as they relate to nadofaragene firadenovec.

1 (Suggests Lower Value)	2 (Intermediate)	3 (Suggests Higher Value)
Uncertainty or overly favorable model assumptions creates significant risk that base-case cost-effectiveness estimates are too optimistic		Uncertainty or overly unfavorable model assumptions creates significant risk that base-case cost-effectiveness estimates are too pessimistic
2 votes	***7 votes***	2 votes

The majority of the Council voted that the model assumptions for nadofaragene firadenovec were neither overly favorable nor unfavorable. The Council based their votes on the high levels of uncertainty in the model, due to the lack of available data and how the model favors highly unstable longer-term outcomes. There is also uncertainty in the assumption that the hypothetical comparator has a 0% response rate.

12. Please vote 1, 2, or 3 on the following potential other benefits and contextual considerations as they relate to oportuzumab monatox.

1 (Suggests Lower Value)	2 (Intermediate)	3 (Suggests Higher Value)
Uncertainty or overly favorable model assumptions creates significant risk that base-case cost-effectiveness estimates are too optimistic		Uncertainty or overly unfavorable model assumptions creates significant risk that base-case cost-effectiveness estimates are too pessimistic
2 votes	***7 votes***	1 vote

The majority of the Council voted that the base-case model assumptions were neither overly favorable nor unfavorable for oportuzumab monatox, for the same reasons as discussed in the previous question. Please note that one Council member was not available to vote on this question.

13. Please vote 1, 2, or 3 on the following potential other benefits and contextual considerations as they relate to nadofaragene firadenovec.

1 (Suggests Lower Value)	2 (Intermediate)	3 (Suggests Higher Value)
Very similar mechanism of action to that of other active treatments		New mechanism of action compared to that of other active treatments
0 votes	3 votes	***7 votes***

The majority of the Council voted that nadofaragene firadenovec represents a new mechanism of action, because of its novel delivery mechanism compared to existing treatments. Please note that one Council member was not available to vote on this question.

14. Please vote 1, 2, or 3 on the following potential other benefits and contextual considerations as they relate to oportuzumab monatox.

1 (Suggests Lower Value)	2 (Intermediate)	3 (Suggests Higher Value)
Very similar mechanism of action to that of other active treatments		New mechanism of action compared to that of other active treatments
0 votes	3 votes	***7 votes***

The majority of the Council voted that oportuzumab monatox represents a new mechanism of action, again because of its novel mechanism of delivery into the cell compared to existing treatments and to nadofaragene firadenovec. Please note that one Council member was not available to vote on this question.

15. Please vote 1, 2, or 3 on the following potential other benefits and contextual considerations as they relate to nadofaragene firadenovec.

1 (Suggests Lower Value)	2 (Intermediate)	3 (Suggests Higher Value)
Delivery mechanism or relative complexity of regimen likely to lead to much lower real-world adherence and worse outcomes relative to an active comparator than estimated from clinical trials		Delivery mechanism or relative simplicity of regimen likely to result in much higher real-world adherence and better outcomes relative to an active comparator than estimated from clinical trials
0 votes	3 votes	***7 votes***

The majority of the Council voted that the relative simplicity of the treatment regimen for nadofaragene firadenovec is likely to result in much higher real-world adherence and better outcomes relative to other treatment options. Earlier in the discussion, one patient expert emphasized that the infrequent instillation schedule for nadofaragene firadenovec could provide a benefit for patients, who previously had to receive frequent instillations of BCG or other agents. One clinical expert also noted that the intensity of instillation schedules for existing treatments has a negative impact on adherence, particularly in rural communities. Please note that one Council member was not available to vote on this question.

16. Please vote 1, 2, or 3 on the following potential other benefits and contextual considerations as they relate to oportuzumab monatox

1 (Suggests Lower Value)	2 (Intermediate)	3 (Suggests Higher Value)
Delivery mechanism or relative complexity of regimen likely to lead to much lower real-world adherence and worse outcomes relative to an active comparator than estimated from clinical trials		Delivery mechanism or relative simplicity of regimen likely to result in much higher real-world adherence and better outcomes relative to an active comparator than estimated from clinical trials
0 votes	***8 votes***	2 votes

The majority of Council members judged that the treatment regimen for oportuzumab monatox would likely lead neither to higher nor lower real-world adherence than for existing therapies. It was noted that the treatment regimen for oportuzumab monatox is more or less comparable to existing therapies and chemotherapeutics. Please note that one Council member was not available to vote on this question.

17. Please vote 1, 2, or 3 on the following potential other benefits and contextual considerations as they relate to nadofaragene firadenovec

1 (Suggests Lower Value)	2 (Intermediate)	3 (Suggests Higher Value)
Will not significantly reduce the negative impact of the condition on family and caregivers vs. the comparator		Will significantly reduce the negative impact of the condition on family and caregivers vs. the comparator
1 vote	***9 votes***	0 votes

The majority of the Council voted that nadofaragene firadenovec will moderately reduce the negative impact of the condition on family and caregivers. The Council discussed that the less frequent treatment regimen and potential effectiveness in preventing recurrence could benefit families and caregivers, who may be responsible for bringing patients to their appointments. Please note that one Council member was not available to vote on this question.

18. Please vote 1, 2, or 3 on the following potential other benefits and contextual considerations as they relate to oportuzumab monatox

1 (Suggests Lower Value)	2 (Intermediate)	3 (Suggests Higher Value)
Will not significantly reduce the negative impact of the condition on family and caregivers vs. the comparator		Will significantly reduce the negative impact of the condition on family and caregivers vs. the comparator
2 votes	***8 votes***	0 votes

The majority of the Council voted that oportuzumab monatox will moderately reduce the negative impact of the condition on family and caregivers, for similar issues as were discussed above. Please note that one Council member was not available to vote on this question.

19. Please vote 1, 2, or 3 on the following potential other benefits and contextual considerations as they relate to nadofaragene firadenovec and oportuzumab monatox

1 (Suggests Lower Value)	2 (Intermediate)	3 (Suggests Higher Value)
Will not have a significant impact on improving return to work and/or overall productivity vs. the comparator		Will have a significant impact on improving return to work and/or overall productivity vs. the comparator
3 votes	***7 votes***	1 vote

The majority of Council members voted that both treatments will have a moderate impact on the ability of patients to return to work. One clinical expert and council member discussed how if the treatments are effective, patients will be able to reduce their number of visits to the clinic for treatment and surveillance. In addition, one patient expert discussed how the potential complications from a cystectomy can affect the daily lives of patients, so preventing cystectomy could provide a large benefit to productivity.

Key Policy Implications

Following its deliberation on the evidence, the Midwest CEPAC engaged in a moderated discussion with a policy roundtable about how best to apply the evidence on nadofaragene firadenovec and oportuzumab monatox for BCG-unresponsive NMIBC to policy and practice. The policy roundtable members included two patient advocates, two clinical experts, two payers, and two representatives from pharmaceutical manufacturers. The discussion reflected multiple perspectives and opinions, and therefore, none of the statements below should be taken as a consensus view held by all participants. The top-line policy implications are presented below, and additional information can be found in the full report.

Manufacturers

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.

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.

Payers

Clinical Considerations

Patient Eligibility Criteria

a. **Patient population:** Given that trials of nadofaragene firadenovec and oportuzumab monatox included only patients with BCG-unresponsive NMIBC, it would be expected that the FDA labels for both treatments be limited to these patients. BCG-unresponsive NMIBC broadly includes patients with refractory disease while receiving treatment or those with relapsing disease following at least two treatment courses. It is not clear whether the FDA labels will explicitly include "BCG-intolerant" patients, but clinicians are likely to view these patients as potentially eligible for treatment with the newer agents. Payers may therefore wish to consider requiring documentation of a trial of BCG as a criterion for coverage.
b. **Diagnosis:** Patients with BCG-unresponsive NMIBC were required to have had biopsy evidence of 1) carcinoma in situ (CIS) or 2) high grade papillary (Ta) or superficially invasive (T1) disease alone. Patients with CIS could also have Ta/T1 disease.
c. **Exclusion criteria:** Patients whose biopsy showed low/moderate grade Ta/T1 disease alone were excluded from the clinical trials. It is not yet known whether the FDA label will specify the pathological grade of NMIBC.

Step Therapy: As mentioned, it seems likely that the FDA label for the emerging treatments will be limited to patients who are unresponsive to BCG. Given that the evidence base is too limited to be able to distinguish the clinical effectiveness among nadofaragene firadenovec, oportuzumab monatox, pembrolizumab, and standard chemotherapy options (e.g., gemcitabine/docetaxel), the question will arise whether payers should consider "economic" step therapy to seek cost savings. This question is highly pertinent given the dramatic cost differences that are likely to exist between the inexpensive chemotherapy regimens and the newer treatment options.

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.

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.

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.

Researchers

Researchers should compare nadofaragene firadenovec and oportuzumab monatox to other therapies in randomized trials of patients with BCG-unresponsive NMIBC.

Researchers 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.

1. Introduction

1.1 Background

Background

Bladder cancer is the most common cancer involving the urinary system. Overall, bladder cancer is the sixth most common cancer in the United States (US), with approximately 80,000 new cases each year and 17,700 deaths.[1,2] The cells lining the inside of the bladder, the urothelium, account for 90% of bladder cancers in the US. Thus, bladder cancer in this report refers to these urothelial cancers (previously called transitional cell).

Bladder cancer usually presents with blood in the urine (hematuria) that is typically painless and intermittent.[3] Individuals with bladder cancer can also have irritative symptoms such as frequency, urgency, or pain when urinating. In most patients, the cancer is confined to the bladder and is treated with limited surgical removal and local instillation of medicine into the bladder (intravesical therapy). Bladder cancer can have a large effect on patients' lives, particularly if the cancer does not respond adequately to standard therapy. The impact on patients includes the side effects of treatments given, the time and costs of surveillance, and the morbidity and effects on quality of life if definitive surgery is performed to entirely remove the bladder (cystectomy).[4,5] In addition to cystectomy's impact on how people normally void, the surgery also involves removal of the prostate for men and may involve the uterus, ovaries, and anterior vagina for women. This can affect sexual function. The overall cost of health care for those with bladder cancer is estimated to be $4-5 billion annually in the US.[6]

The evaluation of patients with hematuria or urinary symptoms includes a history, physical examination, and tests. Risk factors for bladder cancer broadly include chemical and environmental exposures such as cigarette smoking and chemical carcinogens that are ingested or found in the workplace, as well as genetic abnormalities and chronic bladder irritation.[34] The risk of bladder cancer increases with age and bladder cancer is more common in men than women. Bladder cancer is more common in non-Hispanic whites, but survival for those with bladder cancer is lowest in blacks.[35] It is rare in those younger than 40 years old and diagnosis is most common in the late sixties or early seventies.[36] Thus, testing for bladder cancer should be considered in older individuals with macroscopic (visible to the eye) hematuria, urinary symptoms or asymptomatic microscopic hematuria (only noted on testing) in the absence of already identified causes.[37] Though cytology testing of the urine can identify cancer cells, results can be falsely negative particularly for those with low-grade tumors. As a result, direct examination of the lining of the bladder with a fiberoptic scope test, called a cystoscopy, permits taking biopsy specimens and is the standard way to diagnose bladder cancer.

For those diagnosed with bladder cancer, initial treatment involves a procedure called transurethral resection of bladder tumor (TURBT) to remove identified tumors. Staging focuses on differentiating invasive from localized, non-muscle invasive bladder cancer (NMIBC) and whether it has spread beyond the bladder (metastatic cancer). Subsequent treatment of NMIBC is based upon staging of the TURBT as well as imaging tests, such as computed tomography (CT), to identify cancers in other parts of the urinary system such as the kidneys and ureters (the tubes that drain urine from the kidneys to the bladder).[10] When initially diagnosed, NMIBCs comprise around 70% of bladder cancers and are classified based upon biopsy results as: 1) papillary or polyps extending from the lining into the bladder itself (Ta, about 70%); 2) flat, superficial growths (carcinoma in situ [CIS] or tumor in situ [Tis], about 10%); and 3) tumors growing below the superficial lining cells but not into the deeper muscular layer of the bladder wall (submucosa or lamina propria, or T1, about 20%).[7] NMIBCs are further classified based upon histologic grade (low vs. high).

Primary treatment of NMIBC involves removal of visible cancer with TURBT followed by intravesical therapy for those at increased risk for progression to muscle invasive disease. Bacillus Calmette-Guerin (BCG), an attenuated live form of *Mycobacterium bovis*, is the standard initial intravesical therapy. Due to limited and variable supplies of BCG, intravesical chemotherapy treatments are also used.[8] An initial course of therapy involves repeated instillations via a catheter into the bladder. If a response is seen, subsequent maintenance treatment is provided, usually on a less intense schedule. BCG and other intravesical treatments all cause bladder irritation that commonly results in pain, urinary frequency, and urgency. Moreover, these treatments require doctor visits on a weekly or monthly schedule depending on whether it is initial or maintenance treatment.

Though the prognosis for NMIBC is good, and available treatment with BCG or other intravesical therapy in addition to TURBT is effective, many patients will experience a recurrence.[9] In patients with NMIBC, cystectomy is usually curative, but given its morbidity and the decrease in quality of life after the procedure, many patients prefer to accept some risk of cancer progression rather than undergo cystectomy. For those with recurrence long after completing treatment, retreatment with BCG is the standard of care. However, for those with BCG-unresponsive disease, meaning they have progression during treatment with BCG (refractory disease) or relapse soon after stopping therapy, current treatment guidelines include use of other intravesical treatment used alone or in combination, and for those at high risk of progression, consideration of cystectomy.[10] Instillations of chemotherapeutic agents such as gemcitabine (an antimetabolite) either alone or alternating with another chemotherapeutic agent (docetaxel, a taxane) are commonly used,[11] and the systemically-administered immunotherapy agent pembrolizumab (Keytruda®) that was first approved for advanced bladder cancer and was subsequently approved for NMIBC (BCG-unresponsive CIS disease) in January 2020.[12]

Current therapies for BCG-unresponsive NMIBC are not successful in many patients, either due to lack of initial response, side effects, or loss of effectiveness over time. Given this, there is a need for new bladder-preserving treatments in those with BCG-unresponsive NMIBC.[11]

Interventions

Nadofaragene Firadenovec

Nadofaragene firadenovec (Adstiladrin®) uses a nonreplicating recombinant adenovirus vector that encodes the human interferon alfa-2b gene.[13] Adenovirus is a virus that causes the common cold and has been modified to introduce a gene for interferon, a protein made by the body that it uses to fight infections or cancer cells. Nadofaragene firadenovec uses Syn3, a polyamide surfactant, to enhance transfer of the recombinant adenovirus into cancer cells.[14] When the viral vector inserts the gene into the bladder cancer cells, this stimulates the cells to produce interferon that can then kill the cancerous cell. It is instilled as an intravesical treatment every three months. The Biologics License Application (BLA) seeking approval for the treatment of BCG-unresponsive NMIBC for nadofaragene firadenovec was accepted for priority review on 11/25/2019. However, the FDA issued a Complete Response Letter on 05/31/2020 requesting additional information regarding manufacturing.

Oportuzumab Monatox

Another new target for intravesical treatment is the epithelial cell adhesion molecule (EpCAM) positive cancer cell.[38] Oportuzumab monatox (Vicineum®) is an antibody-drug conjugate which combines a monoclonal antibody specific for EpCAM on the surface of tumor cells with an agent that can kill the cells.[15] A recombinant fusion protein with a humanized anti-EpCAM single-chain antibody is linked to a bacterial toxin, *Pseudomonas* exotoxin A. Oportuzumab monatox uses the EpCAM antibody to bind to the cancer cell and then releases the toxin into the cell, inducing cell death (apoptosis). It is instilled twice a week for six weeks, then weekly for six weeks (induction phase). Patients who were disease-free at three months received maintenance instillations every two weeks for up to two years. A rolling BLA submission seeking approval for the treatment of BCG-unresponsive NMIBC for oportuzumab monatox was submitted on 12/9/2019 and is expected to be complete in late 2020.

1.2 Scope of the Assessment

The assessment is described on the following pages using the PICOTS (Population, Intervention, Comparators, Outcomes, Timing, and Settings) framework. Evidence was abstracted from randomized controlled trials and single-arm trials as well as high-quality systematic reviews; high-quality comparative cohort studies as well as retrospective case series were considered, particularly for long-term outcomes and uncommon adverse events (AEs). Our evidence review included input from patients and patient advocacy organizations, data from regulatory documents, information submitted by manufacturers, and other grey literature when the evidence meets ICER standards (for more information, see ICER's grey literature policy).

All relevant evidence was synthesized qualitatively or quantitatively. Wherever possible, we sought out head-to-head studies of the interventions and comparators of interest. We also considered combined use of direct and indirect evidence in network meta-analyses of selected outcomes.

Populations

The population of focus for the review is adults with BCG-unresponsive, high risk NMIBC. This includes patients with biopsy findings showing CIS ± Ta/T1 (population 1) or non-CIS with high grade (HG) Ta/T1 (population 2).

Unresponsive populations include both patients whose cancers did not respond to a reasonable course of treatment with BCG or other chemotherapeutics and patients whose cancers recurred after treatment within a short period of time (6-12 months).[16]

Interventions

The following new intravesical therapies were evaluated:

- Nadofaragene firadenovec (Adstiladrin®)
- Oportuzumab monatox (Vicineum®)

Comparators

We compared nadofaragene firadenovec and oportuzumab monatox to each other and to other bladder-preserving therapies:

- Systemic pembrolizumab (Keytruda®)
- Intravesical therapy with gemcitabine with or without (±) docetaxel

Outcomes

We looked for evidence on the following outcomes of interest:

Efficacy Outcomes:

- Complete response
- Duration of response
- Recurrence-free survival (including type of recurrence, e.g., T1)
- Progression-free survival
- Disease-free survival
- Event-free survival
- Health-related quality of life

- Mortality
- Cystectomy
- Metastatic disease
- Recurrence requiring repeat treatment
- Sexual function
- Treatment burden
- Employment-related outcomes

Safety Outcomes:

- Serious adverse events
- Adverse events leading to discontinuation
- Treatment-emergent adverse events (e.g.)
    - Infection
    - Lower urinary tract symptoms
    - Incontinence
    - Systemic side effects
- Development of antibodies to adenovirus
- Shedding of adenovirus

1.3 Definitions

There are varying ways to define the population of patients with BCG-unresponsive, non-muscle invasive bladder cancer (NMIBC), and these definitions have changed over time.[11] The following is a list of common definitions that are used.

BCG unresponsive refers to patients with: 1) persistent high-grade disease at six months despite adequate BCG (at least five of six induction instillations and at least one maintenance dose [two of three instillations] in a six-month period), 2) any stage or grade progression within the first three months after the first BCG cycle, or 3) recurrence of high-grade disease after achieving a disease-free state at six months after adequate BCG and within six months of the last BCG exposure.[11,39] A fourth group includes patients with persistent or recurrent CIS within 12 months for whom two courses of BCG (or adequate BCG) have failed.[40] Broadly, BCG unresponsive includes those with BCG refractory and relapsing disease.

BCG failure refers to NMIBC that recurs or progresses within six months of BCG therapy.[41] This is a broader definition that includes BCG-unresponsive disease as well as other reasons for failing BCG treatment. These subclassifications were defined by O'Donnell and Boehle as follows:[42]

- **BCG refractory** refers to a failure to achieve a disease-free status within the first six months after induction BCG with maintenance or retreatment.

- **BCG resistant** refers to a recurrent or persistent lower stage/grade tumor at three months with a complete response at six months.

- **BCG relapsing** includes recurrence of disease after a disease-free status was achieved within six months.

- **BCG intolerant** refers to disease recurrence after an inadequate treatment course due to serious adverse effects or symptomatic intolerance.

The most common outcomes reported in the trials of NMIBC are complete response (CR) and high-grade recurrence free survival (HGRFS).

Complete response is the primary outcome when patients have active disease at study entry and is defined as a negative urine test for cancer cells, a normal bladder appearance on cystoscopy and/or biopsy results showing disappearance of cancer cells.[39] Since patients with Ta/T1 only disease will have had resection of the tumor with a TURBT prior to study entry, this definition does not apply.

The FDA defines complete response as either: 1) negative cystoscopy and urine cytology or 2) positive cystoscopy with benign disease on biopsy or low-grade NMIBC and negative cytology at pre-determined time periods (typically 3, 6, 9, and 12 months after initial treatment). https://www.fda.gov/media/101468/download. This FDA definition permits assessing outcomes for all patients and at all follow-up points. In addition, this definition does not include cancer found in the upper tract or prostatic urethra for the intravesical instillation treatments. However, for systemic therapies the presence of urothelial cancer outside of the bladder would lead to considering the patient as not having a complete response.

High-grade recurrence free survival (HGRFS) refers to survival without the reappearance of high-risk disease after the start of therapy.[39] This is most relevant for patients with fully resected high grade papillary disease (Ta) since they have no evidence of disease at study entry and for those who have had a complete response to the study therapy. For the purposes of determining the duration of a complete response, the FDA defines a recurrence as findings on follow-up that no longer meet the above definition for a complete response.

Functional Assessment of Cancer Therapy-General (FACT-G): FACT-G is a patient-reported outcome measure that is commonly used to assess health-related quality of life in cancer patients, covering four domains: physical, functional, emotional, social/family. It offers additional cancer-specific questions that may affect a patient's quality of life (e.g., FACT-BI for bladder cancer patients) (https://www.facit.org/measures/FACT-BI)

Timing

Evidence on intervention effectiveness was derived from studies of at least six months' duration and evidence on harms from studies of at least three months' duration.

Settings

All relevant settings were considered, with a focus on outpatient settings in the US.

1.4 Potential Cost-Saving Measures in NMIBC

ICER includes in its reports information on wasteful or lower-value services in the same clinical area that could be reduced or eliminated to create headroom in health care budgets for higher-value innovative services (for more information, see https://icer-review.org/material/2020-value-assessment-framework-final-framework/). These services are ones that would not be directly affected by therapies for NMIBC (e.g., reduction in need for cystectomy), as these services will be captured in the economic model. Rather, we are seeking services used in the current management of NMIBC beyond the potential offsets that arise from a new intervention. During stakeholder engagement and public comment periods, ICER encouraged all stakeholders to suggest services (including treatments and mechanisms of care) currently used for patients with NMIBC that could be reduced, eliminated, or made more efficient. No suggestions were received.

2. Patient Perspectives

2.1 Methods

In developing and executing this report, we received valuable input from individual patients and patient advocacy groups throughout the scoping and evidence development process. We received open input and public comments on our draft scoping document from two patient advocacy groups and five patients treated for bladder cancer. Below we summarize the key insights derived from this input.

2.2 Impact on Patients

Patients with bladder cancer described different personal stories, but they identified common themes that emphasize the need for better therapeutic options, the demands of current treatment, the possible tradeoff between deciding to avoid or delay removal of the bladder (cystectomy) with risking the progression of the cancer, and the impact of bladder cancer on quality of life regardless of whether they keep their bladder or have it removed.

Though some patients derive benefit from existing therapies, many have high-risk NMIBC that does not respond. Even for those whose cancers respond, there is a need for ongoing treatment, and that treatment can subsequently fail for a variety of reasons. For some, the cancer progresses despite treatment or shortly after a pause in the treatment. For others, side effects require patients to stop therapy. The net result is that for many patients with NMIBC that is unresponsive to BCG, there are limited treatment options available that are bladder preserving.

Patients and patient advocacy groups highlighted the deficiencies of currently available treatments for patients with BCG-unresponsive NIMBC. Even for patients with cancers that benefit from BCG, BCG is associated with side effects including burning, sense of urinary urgency, and discomfort in the groin/pelvis. Over time, these side effects can become more severe, sometimes chronic, and can lead to switching to other substances that are instilled into the bladder, but similar side effects are also seen for other available treatments.

Because BCG and all other substances instilled into the bladder do not lead to a cure for most patients, treatment needs to be continued after an induction course for those who have a positive response. This maintenance therapy is burdensome in that it requires regular visits to a doctor's office where the substance is instilled into the bladder and the patient has to wait for up to a few hours before they can void. Many treatments occur several times a week to several times a month, and regular monitoring with cystoscopies and other tests are needed to look for response, recurrence, or progression during treatment and between courses. Since the start of the COVID-19 pandemic, treatment regimens that require fewer office visits are also viewed as less risky.

Patients also face the burden of deciding whether to undergo cystectomy. For all patients with BCG-unresponsive NMIBC, guidelines recommend that doctors discuss the potential role of cystectomy. This is because these patients have localized disease that has not yet spread beyond the bladder. Delaying surgery and instead opting for instillation therapy into the bladder runs the risk of disease progression or even death, whereas cystectomy is likely to be curative in those with only localized cancer. By selecting bladder-preserving treatments, it is possible that progression to metastatic disease may occur and that cystectomy is then no longer a curative option for the patient. The net result is that patients grapple with the stress of a potential tradeoff between the permanent loss of their bladder and some sexual dysfunction with the risk of disease progression and decreasing the possibility of a cure.

Since bladder cancer often affects older individuals with other pre-existing problems, many patients may not be healthy enough to undergo cystectomy. Even for those in whom cystectomy is an option, no one wants to have their bladder removed. Patients emphasized that surgery not only removes the bladder but also the prostate in men and the uterus and ovaries in women. The impact of cystectomy is large, not only for maintaining the ability to normally void, but cystectomy can have a large negative impact on sexual function.

For those considering cystectomy, most will have a urinary diversion where the urine drains through an opening in the side of the abdomen into a bag. There is the possibility of creating a "neobladder" or artificial bladder from a section of the bowel. One patient who had cystectomy with the creation of an artificial bladder described it as not a treatment for the "faint of heart." The patient also emphasized that one needs to be in good physical health to have such a surgery and that for many this "gold standard" treatment may not be an option.

For all these reasons mentioned, patients and patient advocacy groups highlighted the profound impact of BCG-unresponsive NMIBC on quality of life. The rigors of treatment in terms of time and side effects, the burden of treatment decisions, the need for regular surveillance for recurrence or progression, and the uncertainty associated with managing bladder cancer over time – all of these factors place a large burden on patients. Finally, bladder cancer is one of the costliest cancers to treat. Even with insurance coverage, there is a financial burden on patients, not only in terms of out of pocket expenses for the medical treatment, but also for the time and costs involved in travel to treatments and monitoring. For those still working, bladder cancer can result in disability or lost productivity and wages.

2.3 Impact on Caregivers and Families

Similar to patients, bladder cancer can have a major impact on their families and caregivers. The same factors that impact patients – the rigors of treatment in terms of travel and time, the need for regular surveillance for recurrence or progression, and increased difficulty with managing activities of daily living and inability to work or decreased productivity – all of these factors and their cost can also have a significant impact on families and caregivers. This burden may not only fall upon aging spouses, but also children and other family/friends who may have to interrupt their work and personal life to help care for the patient.

3. Summary of Coverage Policies and Clinical Guidelines

3.1 Coverage Policies

As nadofaragene firadenovec and oportuzumab monatox are yet to be approved by the FDA, coverage policies are not widely available for these new therapies. We were able to locate one clinical policy issued by Centene Corporation for nadofaragene firadenovec that will become effective upon its approval by the FDA. The policy states that criteria for initial approval and continuation of therapy will mirror the FDA label for nadofaragene firadenovec.[43]

We were not able to locate any publicly available coverage policies for oportuzumab monatox.

3.2 Clinical Guidelines

Below, we summarize clinical guidelines pertaining to BCG-unresponsive, high-risk NMIBC from the National Comprehensive Cancer Network (NCCN), American Urological Association (AUA) and Society of Urologic Oncology (SUO), and the National Institute for Health and Care Excellence (NICE). Though all three sets of guidelines provide recommendations for low-risk and more advanced disease, we have focused on guidelines relevant to the populations of interest in this review. While it is not yet clear where nadofaragene firadenovec and oportuzumab monatox will fall in the recommended treatment pathways, we anticipate that they will be incorporated similarly to the other instilled therapies.

National Comprehensive Cancer Network, 2020[44]

The NCCN released an update to its Clinical Practice Guidelines in Oncology for Bladder Cancer in July 2020. The guidelines divide treatment recommendations according to non-muscle invasive (Ta, T1, and Tis) and muscle-invasive (≥T2) bladder cancer, and base recommendations on the findings of biopsy and TURBT specimens. They recommend that NMIBC should generally be managed with intravesical therapy, or cystectomy for very high-risk patients who are able to tolerate the procedure.

Patients with recurrent or persistent high-grade Ta, T1, or Tis following treatment with BCG or intravesical chemotherapy should receive a cystoscopy. If the cystoscopy is positive, the patient should undergo a repeat TURBT followed by treatment with intravesical chemotherapy (gemcitabine or mitomycin) or cystectomy.

If residual disease is seen after TURBT, the guidelines recommend that patients with persistent Ta, T1, and Tis disease proceed to cystectomy because it has the best data for cure. For patients with recurrent Ta or T1 disease who are ineligible for or have elected not to undergo cystectomy, clinicians may consider chemoradiotherapy or a clinical trial. Nonsurgical candidates with recurrent Tis with or without papillary tumors may also be treated with pembrolizumab.

American Urological Association and Society of Urologic Oncology, 2016[32]

A multidisciplinary guideline panel formed by the AUA and SUO released joint guidelines for the diagnosis and treatment of non-muscle invasive bladder cancer in 2016 and amended the guidelines in 2020. The guidelines emphasize the importance of predicting risk of recurrence and progression to treat the disease.

The panel strongly recommends that if a patient is high risk and has newly diagnosed CIS, high-grade T1, or high-risk Ta urothelial carcinoma, a clinician should first administer a six-week induction course of BCG. If a patient has persistent or recurrent disease after a second course of BCG, a clinician should offer radical cystectomy. If the patient is ineligible for or chooses not to undergo cystectomy, a clinician may recommend clinical trial enrollment or offer an alternative intravesical therapy. Patients with CIS may also be offered treatment with systemic pembrolizumab at this point.

National Institute for Health and Care Excellence, 2015[45]

NICE released guidelines for the diagnosis and management of bladder cancer in 2015. The guidelines were re-assessed in 2019 and determined to be consistent with the evidence base.

The guidelines suggest that patients with high-risk NMIBC should be offered the choice of intravesical BCG or radical cystectomy. The choice should be made based on a discussion with the patient about the benefits and risks of each treatment.

Patients with recurrent or persistent NMIBC following induction treatment with BCG should be referred to a specialist urology multidisciplinary team. The team may offer radical cystectomy, or further intravesical therapy if the patient is ineligible for or declines to undergo cystectomy.

4. Comparative Clinical Effectiveness

4.1 Overview

To inform our review of the comparative clinical effectiveness of nadofaragene firadenovec and oportuzumab monatox for BCG-unresponsive NIMBC, we systematically identified and synthesized the existing evidence from available clinical studies. Our review focused on clinical benefits, as well as potential harms (treatment-related AEs) of these agents compared to each other and to systemic pembrolizumab and intravesical gemcitabine ± docetaxel. We sought evidence on all outcomes listed in Section 1.2. Methods and findings of our review of the clinical evidence are described in the sections that follow.

4.2 Methods

Data Sources and Searches

Procedures for the systematic literature review assessing the evidence on new therapies for BCG-unresponsive NMIBC followed established best research methods.[46,47] We conducted the review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[48] The PRISMA guidelines include a checklist of 27 items, which are described further in Appendix Table A1.

We searched MEDLINE, EMBASE, Cochrane Database of Systematic Reviews, and Cochrane Central Register of Controlled Trials for relevant studies. Each search was limited to English-language studies of human subjects and excluded articles indexed as guidelines, letters, editorials, narrative reviews, case reports, or news items. We included abstracts from conference proceedings identified from the systematic literature search. All search strategies were generated utilizing the Population, Intervention, Comparator, and Study Design elements described above. The proposed search strategies included a combination of indexing terms (MeSH terms in MEDLINE and EMTREE terms in EMBASE), as well as free-text terms.

To supplement the database searches, we performed manual checks of the reference lists of included trials and systematic reviews and invited key stakeholders to share references germane to the scope of this project. We also supplemented our review of published studies with data from conference proceedings, regulatory documents, information submitted by manufacturers, and other grey literature when the evidence met ICER standards (for more information, see https://icer-review.org/methodology/icers-methods/icer-value-assessment-framework-2/grey-literature-policy/). Where feasible and deemed necessary, we also accepted data submitted by manufacturers "in-confidence," in accordance with ICER's published guidelines on acceptance and use of such data (https://icer-review.org/use-of-in-confidence-data/).

Study Selection

We included evidence on nadofaragene firadenovec, oportuzumab monatox, and pembrolizumab from all relevant published clinical studies irrespective of whether they used a comparative study design. With respect to gemcitabine ± docetaxel, retrospective studies were also included. Phase I trials were also included if the study included more than 10 patients in the target population and reported clinical outcomes of interest. We excluded abstracts which reported duplicative data available in published articles.

Data Extraction and Quality Assessment

Two reviewers extracted key information from the full set of accepted studies. We used criteria employed by the US Preventive Services Task Force (USPSTF) to assess the quality of clinical trials. For more information on data extraction and quality assessment, see Appendix D.

Assessment of Level of Certainty in Evidence

We used the ICER Evidence Rating Matrix to evaluate the level of certainty in the available evidence of a net health benefit among each of the interventions of focus (see Appendix D).[49]

Data Synthesis and Statistical Analyses

Data on relevant outcomes were summarized in evidence tables (see Appendix Table D3) and synthesized qualitatively in the body of the review. Based on the lack of availability of sufficiently similar trials, we were unable to conduct quantitative synthesis in the form of meta-analysis or network meta-analysis (NMA) to compare outcomes for nadofaragene firadenovec and oportuzumab monatox.

4.3 Results

Study Selection

Our literature search identified 960 potentially relevant references (see Appendix Figure A1), of which 30 references met our inclusion criteria. Primary reasons for study exclusion included study populations outside our scope, reporting of outcomes not relevant to this review, and conference abstracts or posters reporting data subsequently published in peer-reviewed literature.

Of the 30 references, four references represented three trials of nadofaragene firadenovec. Five references represented three trials of oportuzumab monatox. Five references represented one trial of systemic pembrolizumab. Eleven references represented 11 studies of gemcitabine alone and five references represented five studies of gemcitabine in combination with docetaxel. One

conference abstract of a study of gemcitabine in combination with docetaxel met eligibility criteria for inclusion, but there was insufficient information to categorize outcomes in a similar manner to the other therapies at the time of the report.

Full details of all studies included in our systematic literature review are provided in Appendix D. Key trial details including participant characteristics and clinical benefits are presented below.

Quality of Individual Studies

The three trials of nadofaragene firadenovec and three trials of oportuzumab monatox were non-randomized and lacked a placebo or usual care control group and thus we did not assign any quality rating to these trials. Additional details regarding the specifics of the trials can be found in Appendix D. The limitations, uncertainties, and gaps in evidence of these trials are discussed in the Uncertainties and Controversies section.

Assessment of Publication Bias

To assess for publication bias, we searched for studies completed more than two years ago which would have met our inclusion criteria, and for which no findings have been published. Given the emerging nature of the evidence base for newer treatments, we performed an assessment of publication bias for nadofaragene firadenovec and oportuzumab monatox using the clinicaltrials.gov database of trials. We did not find any evidence for publication bias for completed trials of nadofaragene firadenovec or oportuzumab monatox. However, at the time of this report, only interim data from ongoing studies for both nadofaragene firadenovec and oportuzumab monatox were available and these results have not been published and subject to peer review.

Interventions

Trials of Nadofaragene Firadenovec

We identified three single-arm trials of nadofaragene firadenovec that met our inclusion criteria (Table 4.1).[19,24,50,51] We did not identify any studies directly comparing nadofaragene firadenovec to oportuzumab monatox or to any of the comparators.

Key Trials of Nadofaragene Firadenovec

Phase III NCT02773849

Evidence to inform our assessment of nadofaragene firadenovec was mainly derived from NCT02773849, a Phase III, US-based, open-label, single-arm trial.[19,24] The study enrolled 157 adults with BCG-unresponsive NMIBC with pathologic findings of CIS with or without (±) HG Ta/T1 disease or HG Ta/T1 disease alone.[19] Most patients (96%) received at least two previous courses of BCG

treatment within a 12-month period.[25] Patients underwent cystoscopy every three months; if no evidence of HG disease was detected, a further dose of nadofaragene firadenovec was administered every three months at three, six, and nine months after initial instillation. A biopsy was required in addition to cytology and cystoscopy for all patients at 12 months.

Phase II SUO-CTC NCT01687244

NCT01687244 was an open-label, US-based parallel-arm multicenter trial in which patients were randomized to receive intravesical nadofaragene firadenovec at dose of 1 (low dose) or 3 (high dose) $x10^{11}$ vp/mL.[50] The study enrolled 40 adults with BCG-refractory or relapsed NMIBC with CIS ± HG Ta/T1 disease or HG Ta/T1 disease alone. BCG-refractory was defined as no response to BCG after six months. BCG relapse was defined as a recurrence within one year after a CR to adequate BCG treatment. Patients underwent cystoscopy every three months; if no HG recurrence was observed, patients were retreated at months three, six, and nine after initial treatment.

Phase I Dinney 2013

In this open-label, dose-escalating, US-based multicenter Phase I trial, 17 adults with recurrent NMIBC after BCG with CIS ± HG Ta/T1 or Ta/T1 alone were given a single treatment of intravesical nadofaragene firadenovec ($3×10^9$ to $3×10^{11}$ vp/mL) and assessed for toxicity, gene transduction, and CR at three months.[51]

Table 4.1. Trials of Nadofaragene Firadenovec

Trials	Dose(s) Evaluated	Inclusion Criteria	Outcomes	Baseline Characteristics
NCT02773849 N=157 Phase III open-label single arm	Intravesical rAd-IFNα/Syn3 $3x10^{11}$ vp/mL every 3 months up to 4 instillations	BCG-unresponsive NMIBC with CIS ± HG Ta/T1 or HG Ta/T1 only; At least 2 prior courses of BCG within a 12-month period	Primary: • CR in CIS ± HG Ta/T1 Secondary: • Durability of CR in patients with CIS ± HG Ta/T1 • Rate and durability of HGRFS in patients with HG Ta/T1 disease • Rate and durability of HG-RFS in patients with HG Ta/T1 disease	Safety population: • 107 (68%) CIS ± HG Ta/T1 • 50 (32%) HG Ta/T1 only • Median age (IQR): 71 years (66-77) • 129 (82%) Male • 146 (93%) White; 8 (5%) Black; 3 (2%) Asian • 6 (4%) had 1 prior BCG course; 151 (96%) had 2+ BCG courses
SUO-CTC NCT01687244 N=40 Phase II randomized open-label parallel arm	rAd-IFNα/Syn3 Dose $1x10^{11}$ vp/mL (low-dose) rAd-IFNα/Syn3 Dose $3x10^{11}$ vp/mL (high-dose)	BCG refractory or relapsed NMIBC with CIS ± HG Ta/T1 or HG Ta/T1 only	Primary: • 3, 6, 9, 12-month HG-RFS	Overall: • 30 (75%) CIS ± HG Ta/T1 • 10 (25%) HG Ta/T1 only • Median age (IQR): 70 years (67-74) • 33 (82.5%) Male • 2 (5%) had 1 prior BCG course; 38 (95%) had 2+ BCG courses
Dinney 2013 N=17 Phase I open-label, dose-escalating	Single treatment of rAd-IFNα/Syn3 ($3×10^{9}$ to $3×10^{11}$ vp/mL)	Recurrent NMIBC after BCG with CIS ± HG Ta/T1 or Ta/T1 only	Primary: • Safety of rAd-IFNα/Syn3 Secondary: • Gene expression and clinical activity at 3 months	• 11 (65%) CIS ± HG Ta/T1 • 6 (35%) Ta/T1 only • Mean age: 68.7 years • 16 (94%) Male

BCG: Bacillus Calmette-Guerin, CIS: carcinoma in situ, CR: complete response, HG: high grade, HGRFS: high-grade recurrence-free survival, IQR: interquartile range, N: total, NMIBC: non-muscle invasive bladder cancer, rAd-IFN/Syn3: recombinant adenovirus delivered interferon alpha 2-b with Syn3, Ta: non-invasive papillary carcinoma, T1: tumor invading sub-epithelial connective tissue (lamina propria)

Clinical Benefits of Nadofaragene Firadenovec

Complete Response

In the Phase III trial of nadofaragene firadenovec, 90 (59.6%) of the overall study participants achieved a CR at three months. Fifty-five (53.4%) of 103 patients with CIS ± HG Ta/T1 achieved a CR at three months, compared to 35 (72.9%) of 48 patients with HG Ta/T1 disease alone (Table 4.2)[19]. CR was not reported in the Phase II trial. In the Phase I trial, 7 (41%) patients achieved a CR at three months (across all doses and subgroups).

High-Grade Recurrence Free Survival

In the Phase III trial of nadofaragene firadenovec, HGRFS in the overall study population was 47.7%, 42.4%, and 30.5% at six, nine, and twelve months, respectively (Table 4.2). For the CIS ± Ta/T1 group, HGRFS was 40.8%, 35.0%, and 24.3% at six, nine, and 12 months. For the HG Ta/T1 group, HGRFS was 62.5%, 58.3%, and 43.8% for the same time periods. In the Phase II trial, HGRFS in the overall study population was 57.5%, 42.5%, 42.5%, and 35.0% at three, six, nine, and 12 months.[19]

Table 4.2. Efficacy Outcomes for Nadofaragene Firadenovec

Trial	Time Point: Months	3	6	9	12*	Duration of response, median (95% CI), months
Phase III NCT02773849	**Complete Response, n (%; 95% CI)**					
	CIS ± Ta/T1 (N=103)	55 (53.4; 43.3-63.3)	NA	NA	NA	9.69 (9.17- NE)
	HG Ta/T1 alone (N=48)	35 (72.9; 58.2-84.7)	NA	NA	NA	NA
Phase III NCT02773849	**High-Grade Recurrence Free Survival, n (%; 95% CI)**					
	Overall (N=151)	90 (59.6; 51.3-67.5)	72 (47.7; 39.5-56.0)	64 (42.4; 34.4-50.7)	46* (30.5; 23.2-38.5)	7.31 (5.68-11.93)**
	CIS ± Ta/T1 (N=103)	55 (53.4; 43.3-63.3)	42 (40.8; 31.2-50.9)	36 (35.0; 25.8-45.0)	25* (24.3; 16.4-33.7)	NA
	HG Ta/T1 alone (N=48)	35 (72.9; 58.2-84.7)	30 (62.5; 47.4-76.0)	28 (58.3; 43.2-72.4)	21* (43.8; 29.5-58.8)	12.35 (6.67-NE)
Phase II SUO-CTC NCT01687244	**High-Grade Recurrence Free Survival, n (%)**					
	Overall (N=40)	23 (57.5)	17 (42.5)	17 (42.5)	14 (35.0)	NA

CIS: carcinoma in situ, N: total, n: number, NMIBC: non-muscle invasive bladder cancer, Ta: non-invasive papillary carcinoma, T1: tumor invading sub-epithelial connective tissue (lamina propria), 95% CI: 95% confidence interval
*12 month HGRFS includes patients (three patients with CIS and two patients with Ta/T1 disease) whose recurrences were identified based solely on biopsy result (not required for other trials included in this review that only required cytology and cystoscopy).[20]
**Median duration of response for the overall population includes a mixture of CR data for CIS and HGRFS for the Ta/T1 population.

Progression to MIBC

In the Phase III trial of nadofaragene firadenovec, 8 (5.3%) of 151 patients in the overall study population progressed to muscle-invasive bladder cancer (MIBC) during the study follow up period. In the CIS ± Ta/T1 group, 5 (4.9%) of 103 patients progressed to MIBC, while 3 (6.3%) of the 48 patients in the HG Ta/T1 only group progressed.[19] Neither the Phase II nor the Phase I trials of nadofaragene firadenovec reported data on disease progression.

Harms of Nadofaragene Firadenovec

In the Phase III trial, 157 patients were evaluated for safety of nadofaragene firadenovec. One hundred forty-six (93%) reported any treatment-emergent AE (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 treatment-related adverse events included one case each of syncope, sepsis, and hematuria. Three patients (1.9%) discontinued due to a treatment-emergent AE (TEAE). Six patients (3.8%) died (4 in CIS ± Ta/T1 and 2 in Ta/T1 alone). Five (3%) deaths were during the long-term follow-up period when the patients were off treatment and 1 (1%) was on-study.[19,24,25]

Table 4.3. Adverse Events in Phase III Trial of Nadofaragene Firadenovec

Adverse Events	n (%)
Treatment-Emergent AE (TEAE)	146 (93)
Treatment-Related AE	110 (70.1)
Grade 3-5 TEAE	29 (18)
Serious TEAE	14 (9)
Death	6 (3.8)
Discontinuation due to TEAE	3 (1.9)

AE: adverse event, n: number, TEAE: treatment-emergent adverse event

Trials of Oportuzumab Monatox

We identified three single-arm trials of oportuzumab monatox that met our inclusion criteria (Table 4.4).[52-54] We did not identify any studies directly comparing oportuzumab monatox to any of the comparators.

Key Trials of Oportuzumab Monatox

VISTA NCT02449239

Evidence to inform our assessment of oportuzumab monatox was mainly derived from interim results from VISTA NCT02449239, a Phase III, open-label, single-arm trial.[52] The study enrolled 133 adults in the US and Canada with BCG-unresponsive (relapsing or refractory within 6-12 months) NMIBC with CIS ± Ta/T1 disease or HG Ta or any grade T1 disease alone. Oportuzumab monatox was instilled twice a week for six weeks, then weekly for six weeks (induction phase). Patients who

were disease-free at three months received maintenance instillations every two weeks for up to two years. Patients were assessed every 13 weeks; a response was defined as negative cytology along with normal cystoscopy or free of HG disease biopsy. At the time of this report, only non-peer reviewed interim results were available from the Phase III study, which we supplemented with data from conference abstracts and data provided by the manufacturer.

NCT00462488

NCT00462488 was a Phase II open-label, parallel-arm trial of two dosing schedules of intravesical oportuzumab monatox (30mg 1x/week for 6 or 12 weeks)[53] followed by a maintenance schedule up to 12 months. The study enrolled 45 adults in the US and Canada with BCG-unresponsive, refractory, relapsed, or intolerant NMBIC with CIS ± Ta/T1. The primary outcome was CR.

Kowalski 2010

Kowalski 2010 was a Phase I open-label, dose-escalating trial of intravesical oportuzumab monatox at increasing doses 1x/week for six weeks.[54] The study enrolled 64 adults in Canada with NMIBC with CIS ± Ta/T1 or Ta/T1 only refractory or intolerant to BCG. Safety, toxicity, and CR were assessed at three months.

Table 4.4. Trials of Oportuzumab Monatox

Trials	Dose(s) Evaluated	Inclusion Criteria	Outcomes	Baseline Characteristics
VISTA **NCT02449239** **N=133** **Phase III open-label single arm**	30 mg intravesical oportuzumab monatox 2x/week for 6 weeks, then weekly for 6 weeks (induction); disease-free patients at 3 months 2x/month for up to 24 months (maintenance)	BCG refractory or relapsing NMIBC with either CIS ± Ta/T1 or any grade Ta/T1 only; At least 2 prior courses of BCG	Primary: CR in CIS ± HG Ta/T1 Secondary: Durability of CR in patients with CIS ± HG Ta/T1 Rate and durability of HG-RFS in patients with HG Ta/T1 disease only	Safety Population: 93 (70%) CIS ± HG Ta/T1 40 (30%) HG Ta/T1 only Mean age (SD): 73.5 years (8.8)) 103 (77%) Male 124 (93%) White; 5 (4%) Black; 3 (2%) Asian; 1 Other (1%) 100% 2+ BCG courses
NCT00462488 **N=45** **Phase II open-label single arm**	30 mg intravesical oportuzumab monatox 1x/week for 6 weeks (cohort 1) or 12 weeks (cohort 2), followed by up to 3 maintenance cycles of 3 weekly instillations every 3 months	BCG unresponsive, refractory, relapsed, or intolerant NMIBC with CIS ± Ta/T1; At least 1 course of BCG	CR	Overall: 26 (58%) CIS only 19 (42%) CIS + Ta/T1 Median age (range): 74 years (41-92) 35 (78%) Male 43 (96%) White Mean BCG cycles (SD): 2.15 (1.7)
Kowalski 2010 **N=64** **Phase I open-label, dose-escalating**	Intravesical oportuzumab monatox 1x/week for 6 weeks with ascending doses from 0.1 to 30.16 mg	BCG refractory or intolerant NMIBC after BCG with CIS, Ta, or T1	CR	30 (47%) Ta; 17 (27%) T1; 17 (27%) CIS 50 (78%) Male Median age: 69 years 64 (100%) White 2 (3%) 0 BCG cycles; 27 (42%) 1 BCG cycles; 35 (55%) 2+ BCG cycles

BCG: Bacillus Calmette-Guerin, CIS: carcinoma in situ, CR: complete response, HG: high grade, HGRFS: high-grade recurrence-free survival, N: total, NMIBC: non-muscle invasive bladder cancer, Ta: non-invasive papillary carcinoma, T1: tumor invading sub-epithelial connective tissue (lamina propria)

Clinical Benefits of Oportuzumab Monatox

Complete Response

In the VISTA trial, outcomes for the entire study population were not reported. Of the 89 evaluable patients with CIS ± Ta/T1 (out of 93 enrolled), a CR was achieved in 36 (40%) at three months. CR rates were 28%, 21%, and 17% at six, nine, and 12 months, respectively.[52] In the Phase II trial, 18 of 45 (40%) patients in the overall study population achieved CR at three months.[53] CR rates were 27%, 18%, and 16% at six, nine, and 12 months, respectively. In the Phase I trial, 24 of 61 (39%) patients in the overall study population achieved CR at three months.[54]

High-Grade Recurrence Free Survival

In the VISTA trial, HGRFS for the 38 evaluable patients with HG Ta/T1 (out of 40 enrolled) was 71%, 58%, 45%, and 42% at three, six, nine, and 12 months (Table 4.5).[20] Two patients with HG Ta/T1 were excluded from the analysis because they did not complete the induction phase. In the Phase I/II trials, HGRFS was not reported.

Duration of Response

In the VISTA trial, median duration of response was 287 days (SD: 154 days) in the CIS ± Ta/T1 group. Median duration of response in the Ta/T1 group was 402 days. Duration of response was not reported in the Phase I/II trials.

Table 4.5. Efficacy Outcomes for Oportuzumab Monatox

Trial	Time Point (Months)	3	6	9	12	24	Duration of Response, Median (95% CI)
VISTA	**Complete Response, n (%)**						
	CIS ± Ta/T1 (N=89)	36 (40.0)	25 (28.0)	19 (21.0)	15 (17.0)	NA	287 days (±154) (9.4 months)
	Ta/T1 alone (N=38)	NA	NA	NA	NA	NA	
	High-Grade Recurrence Free Survival, n (%)						
	CIS ± Ta/T1 (N=89)	NA	NA	NA	NA	NA	NA
	HG Ta/T1 alone (N=38)	27 (71.0)	22 (58.0)	17 (45.0)	16 (42.0)	NA	402 days (13.2 months)
Phase II	**Complete Response, n (%)**						
	Overall (N=45)	18 (40.0)	12 (26.7)	8 (17.8)	7 (15.5)	NA	NA
Phase I	**Complete Response, n (%)**						
	Overall (N=61)	24 (39.0)	NR	NR	NR	NR	NR

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

In the VISTA trial, Kaplan-Meier estimated rates of progression to MIBC was 4% at 12 months and cystectomy rates were 26% in the overall study population.

Harms of Oportuzumab Monatox

As of the 12-month data output (05/29/2019 data cut-off), 117 of 133 patients in the safety cohort (88%) reported a treatment-emergent AE. The most common TEAEs were urinary tract infection

(32%), pain or burning on urination (26%), hematuria (25%), and urinary frequency (17%). Twenty-nine patients (22%) experienced grade 3-5 TEAEs and 19 (14%) were classified as serious TEAEs. The most common serious TEAEs were acute kidney injury (2%), intestinal obstruction (2%), and serious hematuria or urinary tract infection (4%). Four patients (3%) discontinued due to a TEAE or serious TEAE. One death (<1%) was reported by the manufacturer.[26]

Table 4.6. Adverse Events in Phase III Trial of Oportuzumab Monatox

Adverse Events	n (%)
Treatment-Emergent AE (TEAE)	117 (88)
Treatment-Related AE	66 (50)
Grade 3-5 TEAE	29 (22)
Serious TEAE	19 (14)
Death	1 (<1)
Discontinuation due to TEAE	4 (3.0)

AE: adverse event, n: number, TEAE: treatment-emergent adverse event

Comparators

Trials of Pembrolizumab

Phase II KEYNOTE 057

Evidence to inform our assessment of pembrolizumab was mainly derived from Keynote 057 (Table 4.7).[55,56] Keynote 057 is a Phase II, single-arm, open-label, multi-center trial that enrolled adults from sites in North America, Europe, East Asia, and Australia. This study enrolled 102 patients with BCG-unresponsive NMIBC with CIS ± HG Ta/T1 disease (Cohort A) or HG Ta/T1 disease alone (Cohort B, number enrolled not published to date) who declined to undergo or were ineligible for cystectomy. Patients must have had adequate BCG therapy, which was defined as at least five of six doses of initial induction plus either: at least two of three doses of maintenance therapy or at least two of six doses of a second induction course. Of the 102 patients treated with at least one dose of pembrolizumab, 96 patients were evaluated for efficacy.

Patients received 200 mg of pembrolizumab intravenously every three weeks and could be treated for up to 24 months. The treatment and follow-up phase lasted up to five years or until confirmed disease recurrence/progression. Disease assessments were based on an evaluation of local cystoscopy and centrally-assessed urine cytology, imaging, and TURBT/biopsies as clinically indicated. The first disease assessment occurred at 12 weeks and if patients did not achieve CR, treatment was discontinued, and patients entered survival follow-up. Survival follow-up was described as data collection from patients on general disease status, subsequent therapies, and alive/dead status without efficacy assessment data being collected. The second disease assessment occurred at 24 weeks. If high-risk NMIBC was present, patients discontinued treatment and entered survival follow-up. If there was no recurrence or progression at 24 weeks, patients

continued treatment for up to two years and efficacy assessments are to be conducted through year five or until patients recur/progress.

At the time of this report, interim results for Cohort A (CIS ± HG Ta/T1 disease) from this Phase II study were available. These data were supplemented with conference abstracts and data provided by the manufacturer. Enrollment for Cohort B (HG Ta/T1 disease alone) is ongoing, and results were not available at the time of this review.

A reference dataset for pembrolizumab was included in the safety section to reflect the broader safety profile of pembrolizumab in other indications. The reference data set includes 2,799 patients from five trials assessing pembrolizumab in either advanced melanoma or non-small cell lung cancer.[57]

Table 4.7. Trials of Pembrolizumab[56]

Trials	Dose Evaluated	Inclusion Criteria	Outcomes	Baseline Characteristics
KEYNOTE 057 **NCT02625961** **Phase II, Single-Arm, Open-Label, Multi-Center** **Cohort A (n=96)**	Pembrolizumab 200 mg IV every Q3W up to 24 months	BCG unresponsive NMIBC with CIS ± HG Ta/T1 (Cohort A) or HG Ta/T1 only (Cohort B) • Have received adequate BCG treatment • Fully resected at study entry • Declined or ineligible for cystectomy	Primary: • CR Secondary: • Duration of response	CIS ± HG Ta/T1 • Median age (IQR): 73 years (44-92) • 81 (84.4%) Male • 64 (66.7%) White; 0 (0%) Black; 26 (27.1%) Asian; 6 (6.3% other) • Median instillations, n (range): 12 (7-45)

BCG: Bacillus Calmette-Guerin, CIS: carcinoma in situ, CR: complete response, HG: high grade, IQR: interquartile range, n: number, NMIBC: non-muscle invasive bladder cancer, Ta: non-invasive papillary carcinoma, T1: tumor invading sub-epithelial connective tissue (lamina propria)

Clinical Benefits of Pembrolizumab

Complete Response

Ninety-six patients were evaluated for efficacy with a primary endpoint being CR (Table 4.8). CR was defined in this study as negative results for cystoscopy (with TURBT/biopsies as applicable), urine cytology, and computed tomography urography (CTU) imaging.

Thirty-nine (40.6%) patients had a CR at three months (95% CI: 30.7 to 51.1). With the prespecified primary hypothesis of this trial being that pembrolizumab monotherapy will result in a CR rate greater than 20% in this patient population, this endpoint was considered statistically significant by the investigators as the lower bound of the confidence interval exceeds the 20% criterion. Based on

a Kaplan-Meier curve for duration of CR, CR rates were 38%, 28%, 19% and 19% at six, nine, 12, and 15 months, respectively.[21]

Fifty-six (58.3%) patients did not achieve a CR at three months (95% CI: 47.8 to 68.3). Of the 56 patients, 41.7% (95% CI: 31.7 to 52.2) had persistent disease, 6.3% (95% CI: 2.3 to 13.1) had recurrent disease, 9.4% (95% CI: 4.4 to 17.1) had NMIBC stage progression and 1.0% (95% CI: 0.0 to 5.7) had a non-bladder malignancy. No patients had progression to MIBC (≥T2) disease. One patient was non-evaluable.[55,56]

High-Grade Recurrence Free Survival

At the time of this review, data for HGRFS was not reported.

Duration of Response

Keynote-057 had a median duration of response of 16.2 months with a range between 0 and 30.4 months.

Health-Related Quality of Life

One conference abstract, De Wit 2019,[58] reported on exploratory analyses of health-related quality of life (HRQoL) using the Functional Assessment of Cancer Therapy-Bladder Cancer (FACT-BI) scale as well as the general scale (FACT-G). At the data collection cutoff of 39 weeks, 71.1% of patients for FACT-G and 77.8% of patients for FACT-G physical well-being score had either improved or stable scores from baseline. Improvement was defined as greater than seven-point or greater than three-point increase, respectively for each scale. Stability was defined as a change between negative seven and positive seven or negative and positive three points, respectively. It is also reported that HRQoL was stable for patients who achieved a CR.

Table 4.8. Main Efficacy Outcomes of Keynote-057[21,56]

Trial	Time Point: Months	3	6	9	12	15	Median Duration of Response, Months (Range)
Phase II Keynote-057	Complete Response, n (%)						
	CIS ± Ta/T1 (N=96)	39 (40.6)	36 (38)	27 (28)	18 (19)	18 (19)	16.2 (0-30.4)

CIS: carcinoma in situ, N: total number, Ta: non-invasive papillary carcinoma, T1: tumor invading sub-epithelial connective tissue (lamina propria)

Harms of Pembrolizumab

SAEs and Discontinuation[56]

One hundred two patients were evaluated in the safety population (Table 4.9). Ninety-nine (97.1%) patients reported experiencing any AE with the majority being grade 1 to 2 in severity. The most commonly reported AEs were diarrhea, fatigue, and hematuria in 21.6%, 20.6%, and 20.6% of patients, respectively.

SAEs were experienced in 26 (25.5%) patients, with 8 (7.8%) being treatment-related SAEs. Thirty (29.4%) patients reported grade 3-5 AEs. Treatment-related AEs classified as grade 3/4 were reported by 13 (12.7%) patients, with the most frequent being hyponatremia in 3 (2.9%) patients and arthralgia in two (2.0%) patients. 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. No deaths as a result of progressive disease were reported. Ten (9.8%) patients discontinued treatment due to any AE and 4 (3.9%) patients discontinued due to an SAE.

Twenty-one (20.6%) patients reported any immune-mediated AEs and 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. No new indication-specific immune-mediated AEs associated with pembrolizumab were identified in Keynote-057.

In a briefing document, the FDA agrees that the safety profile of Cohort A for this Phase II trial does not identify any new safety signals or changes to the frequency of adverse reactions across its indications and concludes it is well-characterized due to the large clinical development program for pembrolizumab monotherapy, with over 30,000 participants receiving the therapy in clinical trials.[57] The harms reported in Cohort A of Keynote-057 are compared to a Pembrolizumab Reference Safety Dataset (N=2799) in Table 4.9.

Table 4.9. Adverse Events in Phase II Trial of Pembrolizumab[56,57]

Adverse Events	Patients, n (%)	
	Cohort A (N=102)	Pembrolizumab Reference Safety Dataset (N=2799)
Any AE	99 (97.1)	2,727 (97.4)
Treatment-Related AE (TRAE)	67 (65.7)	NR
Any Grade 3-5 AE	30 (29.4)	1,273 (45.5)
Any Serious AE	26 (25.5)	1,042 (37.2)
Death	2 (2.0)	110 (3.9)
Discontinuation due to TRAE	9 (8.8)	NR
Discontinuation due to any AE	10 (9.8)	334 (11.9)
Immune-Mediated AEs and Infusion Reactions		
Any	21 (20.6)	597 (21.3)
Grade 3-5	3 (2.9)	154 (5.5)
Serious AE	5 (4.9)	161 (5.8)

AE: adverse event, N: number, TRAE: treatment-related adverse event

Trials of Gemcitabine with and without Docetaxel

Gemcitabine

We identified 11 trials of gemcitabine, of which eight were single-arm prospective trials,[22,23,59-64] two were randomized controlled trials (RCTs)[65,66] comparing gemcitabine to another agent (mitomycin or BCG), and one was a retrospective chart review (Table 4.10).[67] The trials varied in terms of eligibility criteria, baseline characteristics of patients, treatment doses and schedules, and outcomes measured (Table 4.10), and the majority were not US-based. Notably, four included patients with Ta/T1 disease only,[59,60,65,66] while the remainder were a mix of CIS with and without Ta/T1. None assessed only CIS patients. Of the prospective trials of gemcitabine, three included 60% or more patients with CIS.[22,23,62] Outcomes stratified by tumor grade subgroups were generally not available and are presented in aggregate.

Table 4.10. Trials of Gemcitabine

Trials	Dose(s) Evaluated	Inclusion Criteria	Outcomes	Baseline Characteristics
Sternberg 2013 N=37 (BCG refractory) Retrospective	2,000 mg intravesical gemcitabine 2x/week for 3 weeks	CIS ± HG Ta/T1 or Ta/T1 only NMIBC refractory to BCG	• Complete response • Recurrence free survival	• 29 (78%) CIS ± HG Ta/T1 • 1 (3%) T1 only • 7 (19%) Ta only • Mean age (range): 71 years (63-75) • 27 (73%) Male
Dalbagni 2002 N=18 Phase 1 single arm	500-2,000 mg intravesical gemcitabine 2x/week for 6 weeks	CIS ± HG Ta/T1 or T1 only NMIBC refractory to BCG	• Complete response	• 14 (78%) CIS ± HG Ta/T1 • 4 (22%) T1 only • Median age (range): 74 years (37-86) • 14 (78%) Male
Dalbagni 2006 N=30 Phase II single arm	2,000 mg 2x/week intravesical gemcitabine for 3 weeks	CIS ± HG Ta/T1 or HG Ta/T1 only NMIBC refractory to BCG	• Complete response • Recurrence free survival	• 23 (77%) CIS ± HG Ta/T1 • 7 (20%) HG Ta/T1 only • Median age (range): 70 years (43-89) • 22 (73%) Male
Skinner 2013 N=47 Phase II single arm	2,000 mg intravesical gemcitabine 1x/week for 6 weeks then monthly up to 40 weeks	BCG unresponsive (relapse or refractory to at least 2 courses of BCG) NMIBC with CIS ± HG Ta/T1, HG or low grade (LG) Ta/T1	• Complete response • Recurrence free survival	• 28 (59.6%) CIS ± HG Ta/T1 • 14 (29.8%) HG Ta/T1 only • 5 (10.6%) LG Ta/T1 only • Mean age (SD): 69.3 years (5.4) • 13 (65%) Male
Perdona 2010 N=20 Phase II single arm	2,000 mg intravesical gemcitabine 2x/week for 6 weeks then weekly for e weeks at 3, 6, and 12 months	CIS ± HG Ta/T1 or HG Ta/T1 alone NMIBC and refractory to BCG	• Complete response • Disease progression	• 7 (35%) CIS ± HG Ta/T1 • 13 (65%) HG Ta/T1 only • Mean age (SD): 69.3 years (5.4) • 13 (65%) Male
Allchorne 2014 N=19 Phase II single arm	1,500 mg intravesical gemcitabine 1x/week for 6 weeks	HG Ta/T1 recurrent bladder cancer after at least 6 weeks of BCG	• Recurrence • Time to recurrence	• 19 (100%) HG Ta/T1 • Mean age (SD): 69.8 years (12.9) • 12 (63%) Male

Trials	Dose(s) Evaluated	Inclusion Criteria	Outcomes	Baseline Characteristics
Di Lorenzo 2010 N=40 Phase II RCT gemcitabine vs. BCG	2,000 mg 2x/week for 6 weeks then 1x/week for 3 weeks every 3 months	HG or LG Ta/T1 NMIBC refractory to BCG	• Recurrence free survival	• 29 (72.5%) HG Ta/T1 • 11 (27.5%) LG Ta/T1 • Mean age (SD): 69.4 years (8.4) • 27 (67.5%) Male
Addeo 2010 N=54 Phase III RCT gemcitabine vs. mitomycin	2,000 mg intravesical gemcitabine 1x/week for 6 weeks	Histologically proven transitional cell carcinoma (TCC) of the bladder at stages Ta/T1 of any grade whose disease has either progressed or relapsed after BCG	• Disease-free survival • Progression	• 54 (100%) Ta/T1 of any grade • Median age (SD): 64.9 years (10.5) • 46 (85%) Male
Gunelli 2007 N=40 Phase II single arm	2,000 mg intravesical gemcitabine 2x/week for 6 weeks	LG Ta or LG or HG T1 recurrent TCC of bladder within 6 months of one induction cycle and at least 3 maintenance cycles of BCG	• Event free survival	• 40 (100%) Ta/T1 • Age n (%): <60: 10 (25), 60-74: 17 (42.5), ≥ 75: 13 (32.5) • 38 (92.5%) Male
Bartoletti 2005 N=40 (BCG refractory) Phase II single arm	2,000 mg intravesical gemcitabine 1x/week for 6 weeks	Intermediate or high-risk superficial TCC; subset of 40 patients were refractory to BCG	• Recurrence free survival	NR for the BCG refractory group
Fiorito 2014 N=41 Phase II single arm	2,000 mg intravesical gemcitabine 1x/week for 6 weeks	Intermediate risk NMIBC recurrent after at least one course of BCG	• Complete response • Disease free survival • Progression free survival	NR

BCG: Bacillus Calmette-Guerin, CIS: carcinoma in situ, CR: complete response, HG: high grade, HGRFS: high-grade recurrence-free survival, IQR: interquartile range, LG: low grade, N: total, NMIBC: non-muscle invasive bladder cancer , Ta: non-invasive papillary carcinoma, T1: tumor invading sub-epithelial connective tissue (lamina propria)

Clinical Benefits of Gemcitabine

Complete Response

Three prospective studies of gemcitabine that included patients with CIS ± Ta/T1 reported CRs at three months (Table 4.11). CRs generally increased with decreasing percentage of CIS patients in the study population. In Dalbagni 2006, 23 out of 30 (77%) study participants had CIS and the study

reported a 50% CR at three months.[22] In Skinner 2013, 28 out of 47 (60%) study participants had CIS and the study reported a 40% CR at three months.[68] In Perdona 2010, 7 out of 20 (35%) study participants had CIS and the study reported a 75% CR at three months.[61] Two studies, one prospective and one retrospective reported CR outcomes but did not specify a time point.[62,67] Both reported a 39% CR rate for gemcitabine in study populations with 78% CIS disease.

One prospective study of gemcitabine did not specify tumor grade but reported a CR of 49% at 12 months.[69]

Recurrence-Free Survival

CIS with or without Ta/T1 Disease

Three prospective studies of gemcitabine that included a mix of patients with CIS ± Ta/T1 and only Ta/T1 disease reported recurrence-free survival (RFS, any grade).[22,23,61] For patients with CIS ± Ta/T1, RFS varied greatly from study to study, from 54% at three months[23] to 93% at three months[22] (Table 4.11). RFS declined precipitously over time, with studies reporting 21% to 50% RFS at 12 months [22,23] and 15% to 38% RFS at 24 months.[22,61]

Ta/T1 Disease Alone

Two studies of gemcitabine that included patients with Ta/T1 disease of any grade reported RFS. In one study in patients with any Ta/T1 disease, RFS was 97%, 83%, 72%, and 50% at six, nine, 12, and 24 months, respectively (Table 4.12).[65] In another study with a similar population, RFS was 95%, 82%, and 66% at six, 12, and 24 months, respectively.[60]

One study reported a 42% HGRFS rate at 12 months in patients with high-grade Ta/T1 disease.[59]

Duration of Response

Five studies of gemcitabine that included both patients with CIS ± Ta/T1 and Ta/T1 disease only reported mean duration of response ranging from 3.5 to 6.1 months (Table 4.11).[23,61] One study of gemcitabine that included patients with HG Ta/T1 only reported a median duration of response of 8 months (range 2 to 62 months) (Table 4.12).[59] One study that did not specify the tumor grades of the study participants[69] reported a median 7.5 month duration of response (range 3 to 73 months).

Progression to MIBC

One study of gemcitabine that did not specify the tumor grades of the study participants reported that 1 patient out of 41 (2.6%) progressed to MIBC.[69]

Table 4.11. Main Efficacy outcomes of Gemcitabine: Mix of CIS and Ta/T1 Study Population

Time Point: Months								
Trial	**% CIS ± HG Ta/T1 population**	**Outcome, n (%)**	**3**	**6**	**9**	**12**	**24**	**Median Duration of Response, months**
Dalbagni 2002 (N=18)	78%	Complete response	39% (time point not reported)					NR
Sternberg 2013 (N=37)	78%	Complete response	39% (time point not reported)					NR
Dalbagni 2006 (N=30)	77%	Complete Response	15 (50)	NR	NR	NR	NR	3.6
		Recurrence Free Survival (Any grade)	NR (93)	NR (28)	NR (27)	3 (21)	NR (15)	3.6
Skinner 2013 (N=47)	60%	Complete Response	19 (40)	NR	NR	NR	NR	6.1
		Recurrence Free Survival (Any grade)*	NR (54)	NR (53)	NR (30)	13 (28)	10 (21)	NR
Perdona 2010 (N=20)	35%	Complete Response	15 (75)	NR	NR	NR	NR	NR
		Recurrence Free Survival (Any grade)*	NR (89)	NR (67)	NR (60)	NR (50)	NR (38)	3.5

*Digitized data

CIS: carcinoma in situ, HG: high grade, N: total, NR: no response, Ta: non-invasive papillary carcinoma, T1: tumor invading sub-epithelial connective tissue (lamina propria)

Table 4.12. Main Efficacy Outcomes of Gemcitabine: Ta/T1 Only Study Population

		Time Point: Months					
Trial	Outcome, n (%)	3	6	9	12	24	Median Duration of Response, Months (Range)
Addeo 2010 (N=54)	Recurrence Free Survival (Any Grade)*	NR	NR (97)	NR (83)	NR (72)	NR (50)	NA
Allchorne 2014 (N=19)	High-Grade Recurrence Free Survival	NR	NR	NR	8 (42)	NR	8 (2-62)
Di Lorenzo 2010 (N=40)	Recurrence Free Survival (Any Grade)	NR (97)	NR (80)	NR (70)	NR (53)	NR (19)	3.9
Gunelli 2007 (N=40)	Complete Response (Any Grade)	NR	28 (95)	NR	NR	NR	NR
	Recurrence Free Survival (Any Grade)	NR	37 (95)	NR	30 (82)	14 (66)	NR

*Digitized data

CIS: carcinoma in situ, HG: high grade, N: total, NR: no response, Ta: non-invasive papillary carcinoma, T1: tumor invading sub-epithelial connective tissue (lamina propria)

Trials of Gemcitabine with Docetaxel

We identified four US-based retrospective studies of sequential intravesical gemcitabine and docetaxel (Table 4.13).[18,70-72] All studies included patients with similar induction dosing schedules of 1,000 mg intravesical gemcitabine followed by 37.5-40 mg docetaxel once weekly for six weeks, per the University of Iowa protocol.[73]

Table 4.13. Studies of Sequential Gemcitabine and Docetaxel

Trials	Dose(s) Evaluated	Inclusion Criteria	Outcomes	Baseline Characteristics
Steinberg 2020 **N=276** **Retrospective chart review**	1,000 mg intravesical gemcitabine followed by 37.5 mg docetaxel 1x/week for 6 weeks	BCG unresponsive NMIBC with CIS ± Ta/T1 HG or HG Ta/T1 only	Primary: • Recurrence free survival Secondary: • High-grade recurrence free survival • Progression	• 173 (62.7%) CIS ± HG Ta/T1; 72 (26%) HG Ta/T1; 31 (xx%) LG Ta/T1 • Median age (range): 73 years (43-94) • 224 (81.1%) Male • 241 (83.7%) White • BCG courses: 147 (53.2%) 1; 128 (46.4%) 2+
Daniels 2020 **N=59** **Retrospective chart review**	1,000 mg intravesical gemcitabine followed by 37.5 mg docetaxel 1x/week for 6 weeks	Biopsy-proven BCG (and other intravesical treatment) unresponsive NMIBC with TIS or HG or LG Ta/T1 only; only those who achieved an initial CR were included in the maintenance study cohort	Primary: • Any grade recurrence Secondary: • Progression	• 24 CIS (41%); 28 (47.5%) HG Ta/T1 only; 7 (12%) LG Ta only • Mean age (SD): 72 years (10.4) • 50 (84.7%) Male • 49 (83%) White • Prior agents used: BCG (83%); MMC (22%); Valrubicin (10%) • Mean prior treatments: 11.6
Milbar 2017 **N=25 (BCG unresponsive or relapsing)** **Retrospective chart review**	1,000 mg intravesical gemcitabine followed by 37.5 mg docetaxel 1x/week for 6 weeks	BCG unresponsive or relapsing NMBC with CIS ± HG Ta/T1 or any grade Ta/T1	Primary: • Any grade recurrence Secondary: • Progression	• 14 (56%) CIS ± HG Ta/T1; 8 (32%) HG Ta/T1 only; 2 (12%) LG Ta only • Mean age (SD): 73 years (10.8) • 20 (80%) Male • 21 (80%) White
Steinberg 2015 **N=41 (BCG failure)** **Retrospective chart review**	1,000 mg intravesical gemcitabine followed by 40 mg docetaxel 1x/week for 6 weeks followed by monthly maintenance instillations	BCG refractory or relapsing NMIBC with CIS ± HG Ta/T1 or any grade Ta/T1	Primary: • Any grade recurrence	Overall: • 29 (64%) CIS ± HG Ta/T1; 12 (27%) HG Ta/T1; 4 (9%) LG Ta • Mean age (SD): 73 years (10.8) • 20 (80%) Male • 21 (80%) White • Median BCG courses: 2 (range: 0-4)

BCG: Bacillus Calmette-Guerin, CIS: carcinoma in situ, CR: complete response, HG: high grade, HGRFS: high-grade recurrence-free survival, IQR: interquartile range, LG: low grade, N: total, NMIBC: non-muscle invasive bladder cancer, Ta: non-invasive papillary carcinoma, T1: tumor invading sub-epithelial connective tissue (lamina propria)

Clinical Benefits of Gemcitabine with Docetaxel

CR was not reported in any of the identified studies of gemcitabine with docetaxel.

High-Grade Recurrence Free Survival

Three studies reported HGRFS among patients with CIS or HG papillary disease (Table 4.14).[18,70,71] Only one study reported HGRFS in subgroups of CIS and HG Ta/T1 disease only, the others only reported HGRFS in the overall study population.[18] In Steinberg 2020, HGRFS for the CIS patients was 75% at six months but declined to 60% at 12 months and 50% at 24 months. In the HG Ta/T1 only population, HGRFS was 87% at six months, but declined to 69% at 12 months and 58% at 24 months. Two studies with patient populations with a mix of CIS and HG and LG Ta/T1 only reported HGRFS at 12 and 24 months.[70,71] In Daniels 2020, 41% of the participants had CIS disease and the study reported a HGRFS of 53% at 12 months and 35% at 24 months. In Milbar 2017, 56% of the participants had CIS disease and the study reported a HGRFS of 51% at 12 months and 34% at 24 months.

One study reported 46% RFS at 12 months in the overall study population (64% CIS).[72]

Table 4.14. High-Grade Recurrence Free Survival in Retrospective Studies of Gemcitabine with Docetaxel

	HGRFS (%) by Time Point			
Trial	**Tumor type**	**6 Months**	**12 Months**	**24 Months**
Steinberg 2020	Any CIS	75%	60%	50%
	HG Ta/T1 only	87%	69%	58%
Daniels 2020	Overall (41% CIS)	NR	53%	35%

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

Progression to MIBC

One study reported data on progression to MIBC.[18] At two years, 11 patients (4%) in the overall study population (a mix of BCG unresponsive, relapsing, intolerant, and unspecified BCG failure patients) had progressed to MIBC.

Mortality

Bladder-cancer specific mortality was reported in three studies. Estimates of bladder-specific mortality varied from 3% at one year and 6% at two years[71], 9% at 15 months[72], and 4% at two years.[18]

Harms of Gemcitabine with and without Docetaxel

Studies of gemcitabine did not report AEs in a consistent way and the estimates varied. Four studies reported AEs of any kind, with results of 38%[66], 39%[65], 67%23, and 71%.[67] The most common AEs were dysuria (9-30%),[22,61,65] hematuria (3-28%),[22,62,65] and urinary tract infection (3-6%).[22,62] One study reported that 12% of patients discontinued treatment due to AEs.[67]

Similarly, AEs were not consistently reported in the studies of gemcitabine and sequential docetaxel. One study reported that 41% of patients experienced side effects from treatment.[18] Nine percent had their treatment schedule affected by side effects. The most common side effects were dysuria (15.6%), hematuria (10.5%), and urinary symptoms (frequency/urgency/retention) (23.5%).

Heterogeneity and Subgroups

Subgroup Analyses

Intensity of Prior BCG Treatment

Prior studies have reported that the intensity of prior BCG treatment in terms of the number of courses is associated with outcomes of therapy for those with BCG-unresponsive NMIBC. In a recent meta-analysis of bladder-preserving treatments of NMIBC, outcomes for patients who received at least one prior course of BCG treatment were better than for those who had undergone two or more prior BCG treatments.[74]

Data on CR and HGRFS by prior BCG treatment subgroups are available for oportuzumab monatox but not nadofaragene firadenovec. In the Phase III VISTA trial, CR rates and HGRFS at three, six, nine, 12, and 24 months were higher for the patients who had received two prior BCG cycles compared to those who had three or more prior BCG cycles. However, the confidence intervals around these estimates were large and, in many cases, overlapping (Table 4.15).

Table 4.15. Efficacy Outcomes of Oportuzumab Monatox by BCG Treatment Subgroups in Phase III VISTA Trial

Time Point: Months	3	6	9	12	24	Median Duration of Response
Complete Response Rate, n (%), 95% CI of %, CIS ±Ta/T1 Population						
2 Prior BCG Cycles (n=42)	16 (38), 24-54	14 (33), 20-50	12 (29), 16-45	9 (21), 10-37	NR	Not reached (95% CI: 273.0 days – N/E; range: 106-644 days)
≥3 Prior BCG Cycles (n=47)	20 (43), 28-58	11 (23), 12-38	7 (15), 6-28	6 (13), 5-26	NR	160.5 days; 5.35 months (95% CI: 96.0 days – 290.0 days; range: 89-651 days)
High-Grade Recurrence Free Survival, % (95% CI) (Kaplan-Meier Estimate), Overall Population						
2 Prior BCG Cycles (n=65)	51 (38-63)	44 (32-57)	37 (25-49)	31 (19-43)	27 (16-39)	NR
≥3 Prior BCG Cycles (n=68)	49 (37-61)	35 (24-47)	26 (16-37)	26 (16-37)	15 (6-24)	NR

BCG: Bacillus Calmette-Guerin, CI: confidence interval, HG: high grade, HGRFS: high-grade recurrence-free survival, IQR: interquartile range, n: number, NR: no response

Percentage of BCG-Unresponsive NMIBC Patients due to Refractory or Relapsing Disease

Patients with BCG-unresponsive NMIBC broadly include individuals whose disease has not responded to therapy (refractory) or who responded but then relapsed shortly after completing a course of therapy. Evidence suggests that BCG-relapsing disease is associated with better outcomes than BCG-refractory disease.[74,75] Trials of nadofaragene firadenovec and oportuzumab monatox have not reported on the percent of enrolled patients who had BCG-refractory or relapsing disease nor their respective outcomes.

Uncertainties and Controversies

For patients with BCG-unresponsive NMIBC, nadofaragene firadenovec and oportuzumab monatox were evaluated in single-arm trials. The lack of comparative data limits the ability to compare these new agents to each other and to other available therapies. The FDA permitted single-arm trials because randomizing patients to placebo or minimally effective therapies was not felt to be ethical, and the only alternative is radical cystectomy.

Guidelines recommend that for patients with BCG-unresponsive NMIBC, physicians discuss that radical cystectomy is the gold standard treatment. Though some may be ineligible for cystectomy due to other existing health conditions that make such surgery too dangerous, most decline cystectomy due to its impact on quality of life. There may be different implications for those who decline cystectomy and are younger and healthier compared to those who are ineligible. Trying

additional bladder-preserving treatments for those who could undergo a potentially curative cystectomy may result in a loss of cure if the cancer progresses. Regardless, for patients with BCG-unresponsive NMIBC who decline or are ineligible for cystectomy, the lack of standard bladder-preserving treatments has led to single-arm trials or investigator-choice therapies that make outcome comparisons difficult.

Feedback received during this project recommended against comparing nadofaragene firadenovec or oportuzumab monatox to each other or to the comparators. Differences in study population, design and outcomes were felt to be too great to compare results. The lack of a placebo or standard treatment group in the Phase III trials examined make this particularly challenging.

In terms of study populations, patient eligibility includes several pathological findings that can lead to differences among trials. NMIBC includes CIS, submucosal invasion (T1) and papillary disease (Ta) which have different outcomes (worse for CIS). For patients with T1 and Ta disease, tumor grade can also vary from low to high. Thus, it is difficult to compare outcomes of studies reporting overall results given enrolled patients have varying proportions of these pathological conditions. One must select studies with similar overall proportions of patients with these pathological findings or look for studies that report outcomes in comparable subgroups.

Studies also defined patients who had failed BCG differently, in ways that may lead to differences in expected treatment outcomes. Heterogeneous patient populations in terms of the proportion who are BCG-refractory, BCG-relapsing, BCG-intolerant, or BCG-unresponsive can cause difficulty in comparing results among trials. For example, failure types such as BCG-relapsing are associated with better outcomes compared with other reasons for BCG failure.

Moreover, the specific prior treatments received and their intensity may also lead to differences among studies. Though BCG-unresponsive NMIBC implies prior use of BCG, the number of instillations per treatment cycle, the number of treatment cycles, and the potential use of other instilled therapies may also lead to differences among studies in terms of patients and how resistant to subsequent treatment their NMIBC is likely to be.

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. Efficacy outcomes were reported for all eligible patients in the nadofaragene firadenovec trial who received study drug, whereas patients who did not complete induction therapy were excluded in the oportuzumab monatox trial. The primary outcome of nadofaragene firadenovec and oportuzumab monatox was CR assessed at similar time intervals, but 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. In addition, for the pembrolizumab trial, but not for nadofaragene firadenovec and oportuzumab monatox trials, CR required absence of upper tract or prostatic urethral cancer.

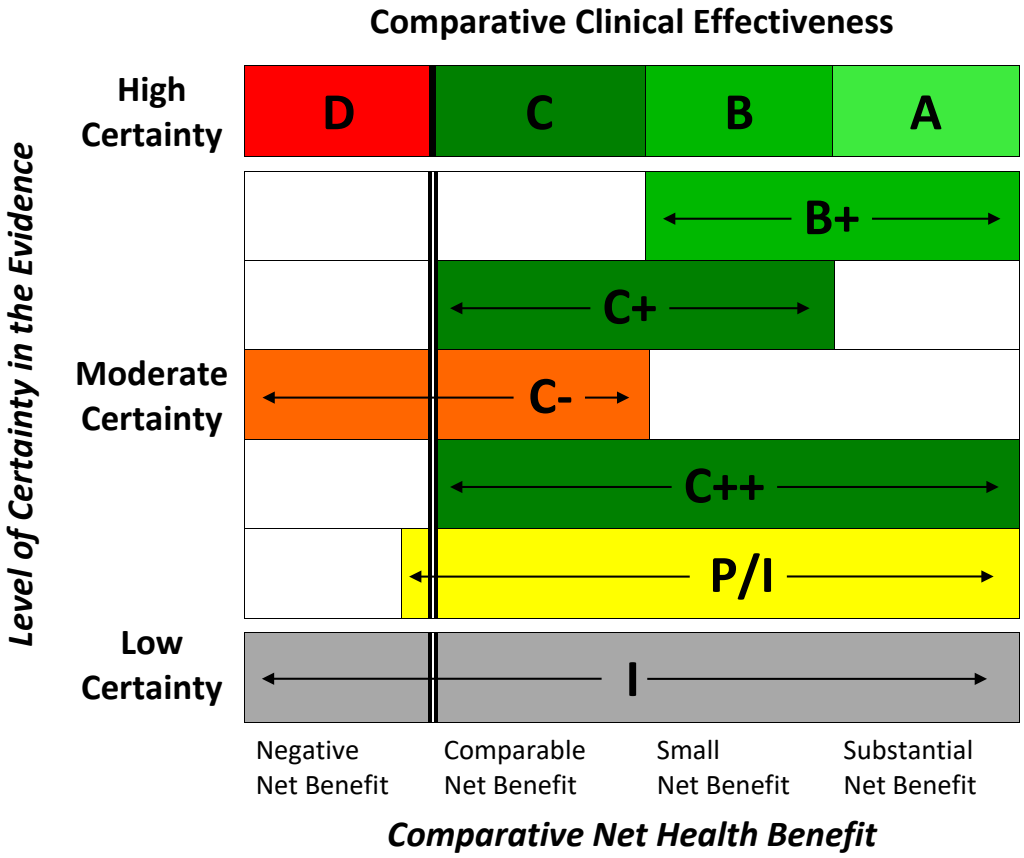
Though outcomes of nadofaragene firadenovec and oportuzumab monatox show response rates that are similar to or better than currently available treatments, there continues to be considerable uncertainty about their efficacy over time. This is particularly important in that most patients receiving nadofaragene firadenovec or oportuzumab monatox either did not have a CR or had recurrence/progression over time. Few patients progressed to metastatic disease or died during the short follow-up period, but it is possible that these treatments may lead to more patients avoiding potentially curative cystectomy and therefore progressing to metastatic disease or dying of bladder cancer. For pembrolizumab, the trial data suggests that the small percent of patients who respond appear to have a durable response, but whether metastatic disease or death are also seen with this drug requires longer term follow-up in more patients.

Pembrolizumab has been used for a variety of cancers and though generally well tolerated, it is given systemically and is associated with infrequent but potentially serious complications. Nadofaragene firadenovec and oportuzumab monatox appear to have few serious side effects and given their administration directly into the bladder, may be safer. Nevertheless, as new therapies, potential side effects of nadofaragene firadenovec and oportuzumab monatox will require longer term evaluation in more patients.

A number of chemotherapeutic drugs instilled into the bladder have been examined for patients with BCG-unresponsive NMIBC. Though valrubicin is FDA approved for this indication, it is rarely used in clinical practice because of its short duration of response. Gemcitabine ± docetaxel is used off-label in patients with BCG-unresponsive NMIBC. Published outcomes appear to have similar responses to those of nadofaragene firadenovec, oportuzumab monatox, and pembrolizumab, but differences in patient populations and study design make any direct comparisons exceedingly difficult. Nevertheless, similar outcomes and expected lower costs of gemcitabine ± docetaxel suggest that trials comparing these older chemotherapeutic drugs with these newer agents are warranted.

4.4 Summary and Comment

Figure 4.1. ICER Evidence Rating Matrix



A = "Superior" *- High certainty of a substantial (moderate-large) net health benefit*
B = "Incremental" *- High certainty of a small net health benefit*
C = "Comparable"- *High certainty of a comparable net health benefit*
D= "Negative"- *High certainty of an inferior net health benefit*
B+= "Incremental or Better" *– Moderate certainty of a small or substantial net health benefit, with high certainty of at least a small net health benefit*
C+ = "Comparable or Incremental" *- Moderate certainty of a comparable or small net health benefit, with high certainty of at least a comparable net health benefit*
C- = "Comparable or Inferior" *– Moderate certainty that the net health benefit is either comparable or inferior with high certainty of at best a comparable net health benefit*
C++ = "Comparable or Better" *- Moderate certainty of a comparable, small, or substantial net health benefit, with high certainty of at least a comparable net health benefit*
P/I = "Promising but Inconclusive" *- Moderate certainty of a small or substantial net health benefit, small likelihood of a negative net health benefit*
I = "Insufficient" *– Any situation in which the level of certainty in the evidence is low*

Figure 4.2 Phase III Results of Nadofaragene firadenovec: Complete Response and High-Grade Recurrence Free Survival, CIS ± Ta/T1 and Ta/T1

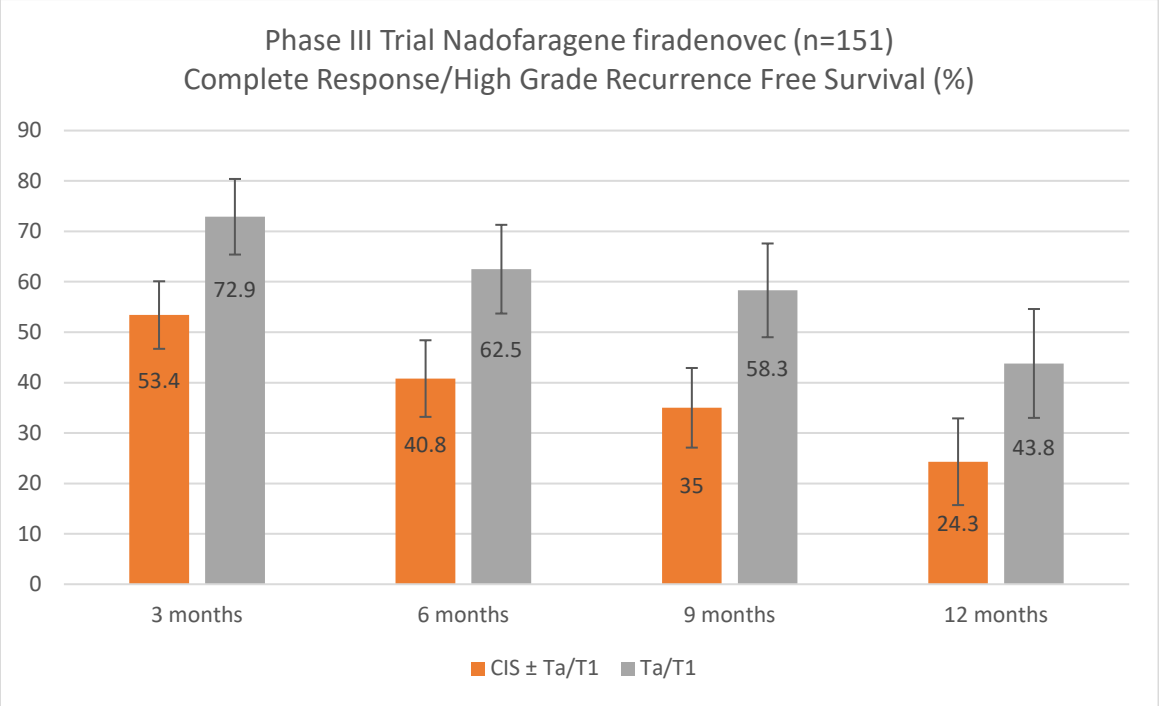


Figure 4.3 Phase III Results of Oportuzumab monatox: Complete Response and High-Grade Recurrence Free Survival, CIS ± Ta/T1 and Ta/T1

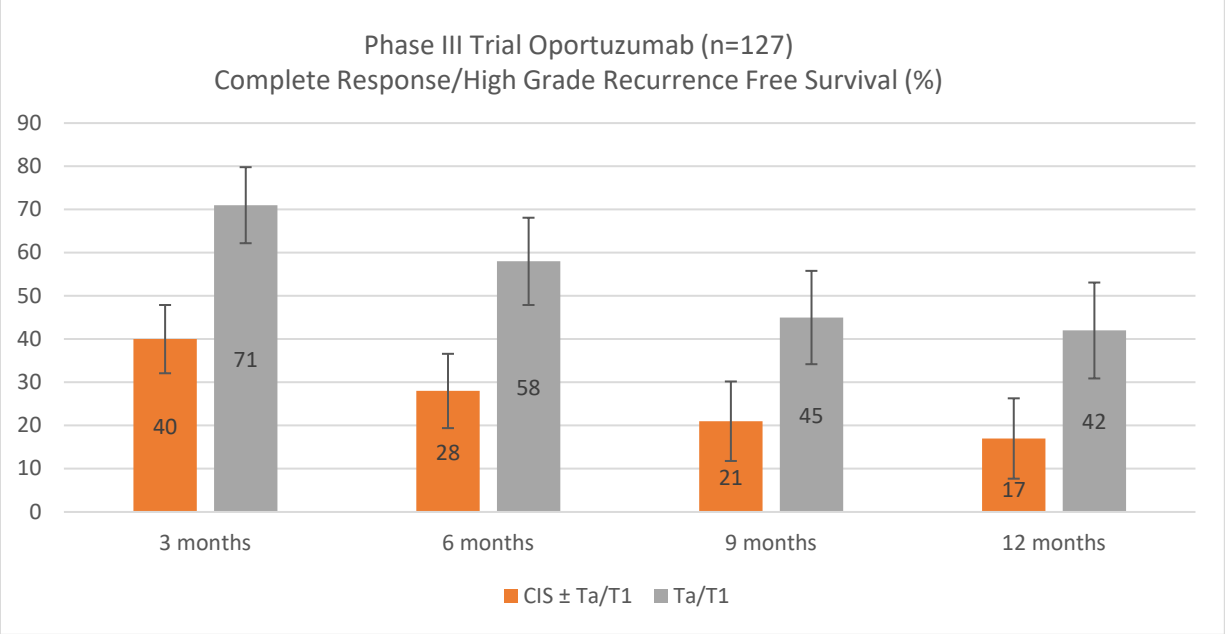
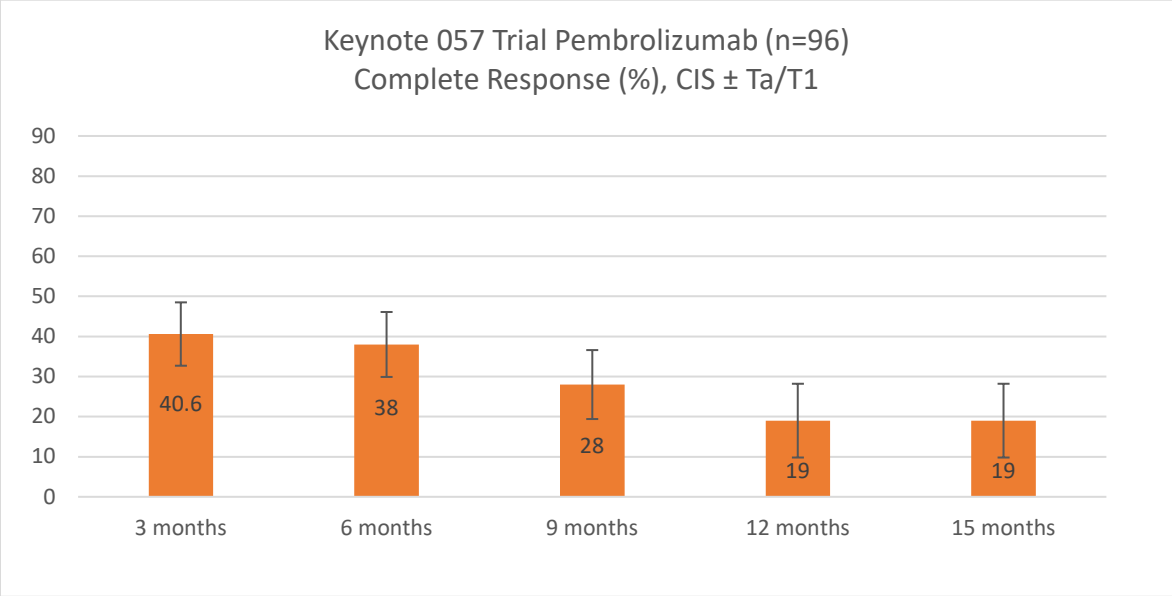


Figure 4.4 Phase II Results of Pembrolizumab: Complete Response, CIS ± Ta/T1



Results from studies of the interventions of interest are presented in Figures 4.2-4.4. 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. By comparison, in the mixed CIS and Ta/T1 study populations for two Phase II studies of gemcitabine, recurrence free survival (of any type) at 12 months was 21-28%[22,23].[22,23] In the retrospective study of sequential gemcitabine and docetaxel, HGRFS at 12 months was 60% in the CIS population and 69% in the HG Ta/T1 population.[18]

Few serious harms were reported and there were low discontinuation rates due to TEAEs (1.9% for nadofaragene firadenovec and 3% for oportuzumab monatox).[19,20,24] In the Phase II trial, 9.8% of patients discontinued pembrolizumab due to any AE. Discontinuations of 9-12% were reported for gemcitabine with or without docetaxel.[18,56,68,76] Nadofaragene firadenovec is given much less frequently than oportuzumab monatox. This is a benefit in itself, especially during the COVID pandemic when patients and caregivers may be reluctant to come for office visits.

The single-arm trials limit the ability to compare nadofaragene firadenovec and oportuzumab monatox to each other and to the comparators. The lack of a placebo or active comparator, though meeting FDA guidance, results in uncertainty about the magnitude of benefit of these new agents. In addition, varied patient populations and histologies, differences in prior treatments, short-term outcomes reported in a relatively small number of individuals, and lack of long-term follow-up limit the ability to reach conclusions about the therapies in comparison with best supportive care, and preclude reaching conclusions comparing the therapies with each other or with the comparator therapies. Finally, since most patients treated with nadofaragene firadenovec and oportuzumab monatox will end up having progression or recurrence over time, it remains to be seen whether

delaying potentially curative therapy with cystectomy leads to greater long-term disease related mortality. The magnitude of any such increase in mortality would be key to assessing the balance between benefits and harms.

As such, we have rated both nadofaragene firadenovec and oportuzumab monatox as "comparable or incremental" ("C++") when compared with best supportive care. 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. Given the large uncertainties about comparative benefits and harms, we have rated comparisons between the interventions with each other and with the comparators of pembrolizumab and gemcitabine ± docetaxel as "insufficient" ("I"). These ratings are shown in Table 4.16.

Table 4.16. Summary of Evidence Ratings for Nadofaragene Firadenovec and Oportuzumab Monatox

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

5. Long-Term Cost Effectiveness

5.1 Overview

The primary aim of the analysis was to evaluate the cost effectiveness of nadofaragene firadenovec and oportuzumab monatox compared with no bladder cancer treatment in BCG-unresponsive NMIBC. Although our initial intent was to include pembrolizumab and gemcitabine ± docetaxel as comparators, given the "I" evidence ratings, direct comparisons were not made with nadofaragene firadenovec and oportuzumab monatox. In the absence of comparative data on which to base our incremental analyses, we chose to evaluate all treatments (including pembrolizumab and gemcitabine ± docetaxel) compared with a hypothetical treatment whose effectiveness at achieving complete response (CR) at 3 months could be varied in sensitivity analyses. For the base case, this hypothetical treatment was completely ineffective, with a CR of 0% at three months. We evaluated the cost-effectiveness of all treatments in two populations. The first population was patients with CIS ± HG Ta/T1 (population 1) and the second population was patients with HG Ta/T1 disease alone (population 2). We developed a *de novo* decision analytic model informed by key clinical trials, prior relevant economic models, systematic literature reviews, and input from diverse stakeholders (patients, advocacy groups, clinicians, payers, researchers, and manufacturers of these agents). For each population, we estimated time in remission, total costs, total quality-adjusted life years (QALYs), total equal value life years gained (evLYGs), and total life years (LYs) for each treatment strategy over a lifetime time horizon. A description of the methodology used to derive the evLYG can be found in Appendix E. The incremental cost-effectiveness ratios for nadofaragene firadenovec and oportuzumab monatox compared with the hypothetical treatment were generated. We also calculated the incremental cost effectiveness of pembrolizumab (for population 1 only) and gemcitabine ± docetaxel (for populations 1 and 2) compared with the hypothetical treatment.

The base-case analysis was conducted using a health care sector perspective. The impact of productivity and other indirect costs were evaluated for inclusion in a modified societal perspective scenario analysis. However, insufficient data on the impact of bladder cancer on indirect costs of care were identified to quantify these potential benefits of therapy. All costs, QALYs, evLYGs, and LYs were discounted at a rate of 3% per annum. The structure of the models, assumptions, data, and results are described in detail in the methods sections below. A reference case checklist, as recommended by the Second Panel on Cost-Effectiveness in Health and Medicine, is shown in Appendix Table E1.[77]

Since the last report, the following changes were made to this version of the report:

- The transition probability for complete response to NMIBC after 12 months was changed in both the CIS ± Ta/T1 and High-Grade Ta/T1 to reflect updates in available data for nadofaragene firadenovec
- The transition probability for NMIBC to MIBC was changed in both the CIS ± Ta/T1 and High-Grade Ta/T1 to reflect updates in available data for nadofaragene firadenovec
- The transition probability for complete response to NMIBC after 12 months was changed in the CIS ± Ta/T1 population to reflect updates in available data for oportuzumab monatox
- The transition probability for complete response to NMIBC at 3, 6, 9, and 12 months was changed in the Ta/T1 population for oportuzumab monatox. Data was provided to replace Kaplan-Meier curve estimates and make the analyses to estimate treatment effectiveness in the first 12 months comparable to those for nadofaragene firadenovec.

5.2 Methods

Model Structure

For the cost-effectiveness analysis, we developed a de novo semi-Markov model with time-varying proportions of patients with high-grade recurrence-free survival (HGRFS) and mortality. A Markov model was chosen as it allows for more transparent assessment of chronic conditions than with some other modeling approaches. In addition, there were sufficient data available to populate the needed model inputs using this approach. The model was developed using Microsoft Excel 365 ProPlus. The model was primarily informed by key clinical trials, prior relevant economic models, systematic literature reviews, and input from diverse stakeholders (patients, advocacy groups, clinicians, payers, researchers, and manufacturers of these agents). The base case used a US health care sector perspective. Costs and outcomes were discounted at 3% annually. The model cycle was three months, based on assessment of treatment response, typical follow-up, and prior models.

The model evaluated two populations of patients with BCG-unresponsive NMIBC: those with 1) CIS ± HG Ta/T1 and 2) HG Ta/T1 alone. In the model, patients in population 1, with CIS ± HG Ta/T1, were treated with nadofaragene firadenovec or oportuzumab monatox. Pembrolizumab and gemcitabine ± docetaxel were included in the model for patients in population 1, but not directly compared with nadofaragene firadenovec or oportuzumab monatox. In the base case, a hypothetical treatment with a 0% CR at 3 months was the comparator for all treatments. Patients in population 2, with HG Ta/T1 alone, were treated with nadofaragene firadenovec or oportuzumab monatox. Gemcitabine ± docetaxel was included in the model for patients in population 2, but not directly compared with nadofaragene firadenovec or oportuzumab monatox. The base case

comparator for all treatments was a hypothetical treatment with a 0% CR at 3 months. The effectiveness of this comparator in achieving CR at three months and maintaining CR (in population 1) or HGRFS (in population 2) was varied for both populations in sensitivity analyses, using a rate ratio, from a CR of 0% to the CR observed for the most effective treatment from clinical trials at three months. The proportion of patients maintaining CR (for population 1) or HGRFS (for population 2) at each time point after month 3 was concurrently varied using the inverse of the rate ratio.

As shown in the model schematic, Figure 5.1, and using the definitions shown in Table 5.1, simulated patients with NMIBC entered the model through the Markov state "Initial Treatment," and received treatment with nadofaragene firadenovec, oportuzumab monatox, pembrolizumab, gemcitabine ± docetaxel, or the hypothetical treatment. Patients transitioned from "Initial Treatment" to "Disease-free" at the end of the first cycle based on the CR rate from clinical trials. Patients who did not get CR from treatment transitioned at the end of the first cycle to "Persistent/Recurrent NMIBC" or to the "Death" Markov state.

In the second and subsequent cycles, patients could transition to all other Markov states. From the "Disease-free" Markov state, patients could move to the "Persistent/Recurrent NMIBC" Markov state. Patients in the "Persistent/Recurrent NMIBC" state could move to the "MIBC" state or have a cystectomy and transition to the "Post-Cystectomy" state. From the "MIBC" state, patients could have a cystectomy and move to the "Post-Cystectomy" state or progress to the "Metastatic Disease" state. Patients may also move from "Post-Cystectomy" to "Metastatic Disease." Finally, patients could move from any state to the "Death" Markov state in any cycle of the model.

Since 100% of patients with CR remained in progression-free survival in the first three months, we restricted patient movement directly from "Disease-free" to "MIBC." Similarly, we restricted the transition from "Disease-free" and "Persistent/Recurrent NMIBC" directly to "Metastatic Disease."

Each cycle, patients could move among the Markov states according to the probabilities listed in the Model Inputs section below. Costs, QALYs, evLYGs, and LYs were accrued depending on the time spent in each Markov state. The method used for estimating evLYG can be found in Appendix E.[78] In addition, cystectomy and short-term mortality costs were accrued during transitions to "Post-cystectomy" and "Death," respectively.

Figure 5.1. Model Framework

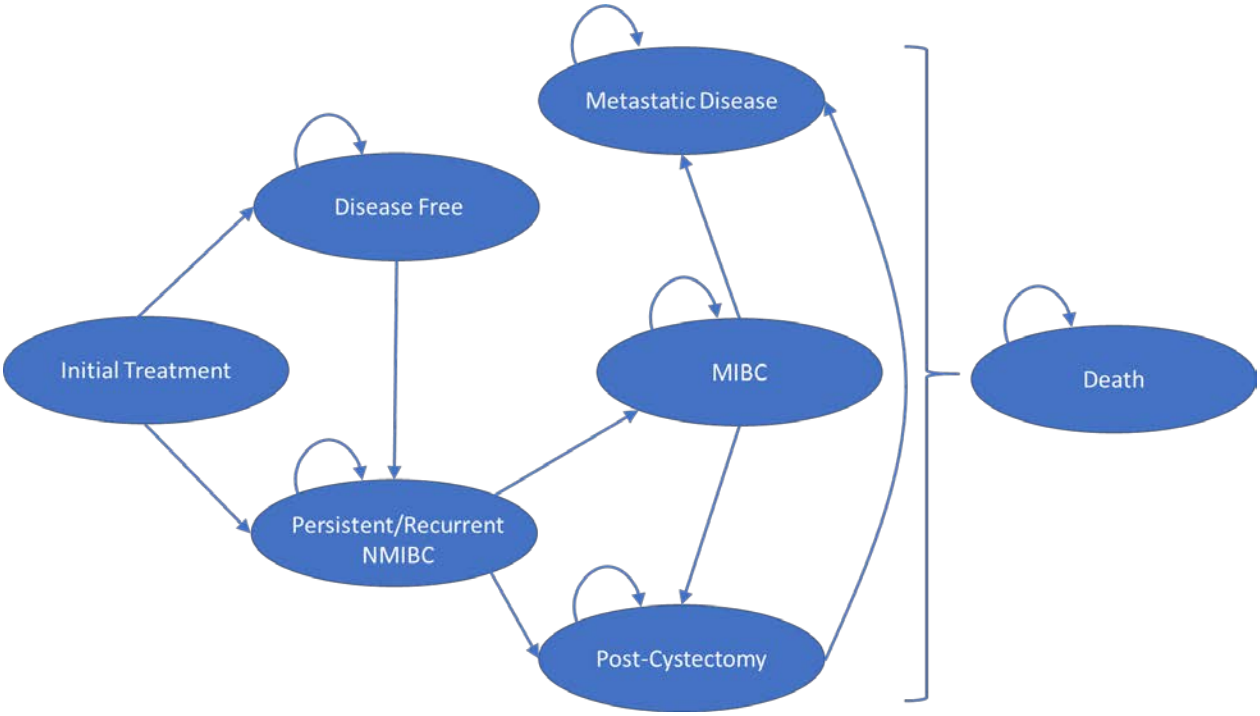


Table 5.1. Treatment Response Definitions Used in the Model

Treatment Response Description	Definition	Calculation from Clinical Trials
Complete Response and Disease-Free	Complete response is defined as negative cystoscopy and negative (including atypical) urine cytology or positive cystoscopy with biopsy-proven benign or low-grade NMIBC and negative cytology. Disease-Free was defined as having achieved CR at month 3 and maintained CR (for population 1) or HGRFS (for population 2) at time points beyond 3 months.	Proportion of all patients who were and remained disease-free at defined time points.
Persistent or Recurrent NMIBC	Persistent was defined as tumors that show continued evidence of symptoms or morphological features, or if a second tumor is diagnosed within three months after therapy was completed. Recurrent was defined as findings on follow-up that no longer meet the above definition for a complete response, but not including progression to MIBC, metastasis, or death.	Proportion of patients without CR in population 1 or HGRFS in population 2 (i.e. 1 – CR or HGRFS).
MIBC	Presence of cancer in the muscle wall of the bladder.	Proportion of patients originally with NMIBC and with progression to MIBC at defined time points.
Post-Cystectomy	State following surgical removal of bladder.	Proportion of patients from clinical trials having had surgical removal of the bladder.
Metastasis	Development of secondary malignant growths at a distance from a primary site of cancer	Proportion of patients originally with NMIBC, MIBC, or having had surgical removal of the bladder and with progression to metastatic disease at defined time points.

NMIBC: non-muscle invasive bladder cancer, CR: complete response, HGRFS: high-grade recurrence-free survival

Target Population

The population of interest for this economic evaluation was the prevalent cohort of individuals in the US with BCG-unresponsive high-risk NMIBC. Two separate subgroups of patients were evaluated. The first subgroup (population 1) were patients who had CIS ± Ta/T1, a superficial bladder cancer that is confined to the surface of the bladder, but that is considered of higher grade and increases the risk of recurrence and progression. The second subgroup (population 2) were patients with HG Ta/T1 disease, which is characterized by polyps extending from the bladder lining but without invasion below the lining (Ta) or with invasion further into the bladder tissue but not as far as the bladder muscle (T1). The general characteristics of the population in each model will

reflect the average patient with BCG-unresponsive NMIBC in the clinical trials, which are shown in Table 5.2.

Table 5.2. Base-Case Model Cohort Characteristics

	Value	Primary Sources
Mean Age (years)	72	FerGene data on file[25] Sesen Bio data on file[20] Stuart 2019[79]
Female	20%	

Treatment Strategies

Interventions included in the model were nadofaragene firadenovec, $3x10^{11}$ vp/mL (75 mL) given intravesically every three months with a mean treatment duration of 10.19 months,[25] and oportuzumab monatox, 30 mg given intravesically twice weekly for six weeks then once weekly for six weeks, then every other week thereafter with a mean treatment duration of 8.1 months.[80] Pembrolizumab was based on the administration of 200 mg IV over 30 minutes every 3 weeks or 400 mg IV over 30 minutes every 6 weeks for up to 24 months, with an estimated mean treatment duration of 6.2 months. Gemcitabine ± docetaxel was based on the administration of gemcitabine 1000 mg, followed by docetaxel 37.5 mg given intravesically once weekly for 6 weeks.[18] As only 3.3% of patients were unable to tolerate the full 6 weeks of treatment and mean treatment duration was not reported, we assumed a 6-week mean treatment duration. For each population, the comparator was a hypothetical treatment. For the base case, the effectiveness of the theoretical treatment was set to a CR probability of 0%. The effectiveness of the hypothetical treatment was varied between completely ineffective to the level of the most effective treatment.

Key Model Characteristics and Assumptions

The model required several assumptions. Key model assumptions and rationales for the assumptions are presented in Table 5.3.

Table 5.3. Key Model Assumptions

Assumption	Rationale
Patients who are disease-free or who have metastatic disease will not have a cystectomy.	Data are not available describing the probability that patients who are disease-free or who have metastatic disease elect to undergo cystectomy. Patients who are disease-free do not require cystectomy unless there is disease progression. Patients with metastatic disease will require systemic rather than local therapy.
States of persistent or recurrent NMIBC have similar utilities and costs.	We have not identified data documenting differences in utility or costs between persistent and recurrent NMIBC.
Utilities for the metastatic state originating from other cancers are similar to the utilities for metastatic bladder cancer.	We were unable to identify utilities for metastatic disease specifically due to bladder cancer. Therefore, we used values obtained from patients with metastatic urothelial carcinoma.
Patients with no treatment have disease progression at the same (average) rate as those from longer-term studies in whom treatment is not effective.	We identified no data informing disease progression in patients who receive no bladder cancer treatment. Most data available are from single-arm studies with active treatment. This assumption is necessary to compare the new treatments to no bladder cancer treatment.
Patients who have a complete response to treatment do not develop MIBC within a 3-month period. Instead they progress to NMIBC, and then to MIBC, over a period longer than the model cycle length.	This assumption makes estimating other probabilities easier in the model, given the limited availability of detailed data on NMIBC progression. The assumption is supported by clinical trials for nadofaragene firadenovec, oportuzumab monatox, and pembrolizumab, in which 100% of patients showed progression-free survival at 3 months.
Patients who have complete response or persistent/recurrent NMIBC do not progress to metastatic disease directly within a 3-month period. Instead, they progress through (NMIBC for those with complete response and) MIBC to metastatic disease.	This assumption makes estimating other probabilities easier in the model, given the limited availability of detailed data on progression to metastatic disease. The assumption is supported by several studies.

NMIBC: non-muscle invasive bladder cancer

Model Inputs

Clinical Inputs

Clinical inputs for the effectiveness of nadofaragene firadenovec, oportuzumab monatox, and pembrolizumab were obtained from single-arm clinical trials evaluating these therapies in the treatment of BCG-unresponsive NMIBC.[18,20,79,81] The effectiveness of gemcitabine ± docetaxel was obtained from a large multicenter noncomparative retrospective evaluation.[18] However, the probability of having high-grade progression free survival with gemcitabine ± docetaxel was unusually high in this study relative to other studies of gemcitabine ± docetaxel.[70-72] Using a conservative approach, we adjusted the proportion of patients with high-grade progression free

survival at each time point using a rate ratio derived from three other trials involving gemcitabine ± docetaxel (resulting RR=0.8).[70-72]

The effectiveness of the hypothetical comparator treatment was added to the model using a risk ratio that was applied to intervention model inputs for CR in the transition from "Initial Treatment" to "Disease-free." The inverse of the same risk ratio was applied to modify the probabilities associated with transitions from "Disease-free" to "Persistent/Recurrent NMIBC," resulting in an increased probability of transitioning to NMIBC. This risk ratio value was limited so that transition probabilities could not exceed a value of one. Varying this risk ratio between 0 and 1 resulted in the effectiveness of the hypothetical treatment varying between completely ineffective to having the same benefit as the most effective treatment. However, because this treatment was a hypothetical treatment, costs and disutility associated with adverse events were not included. The base-case value for the risk ratio was set to zero, meaning that the CR probability at three months was 0.

Clinical Probabilities/Response to Treatment

The decision model was evaluated over a lifetime time horizon with three-month cycles. The probability of moving from "Initial Treatment" to "Complete Response/Disease-free" was determined from CR to treatment at three months from clinical trials.[18,20,79,82]

For population 1, the probability of moving from "Disease-free" to "Persistent/Recurrent NMIBC" was determined from CR, when available, at 6, 9, and 12 months and were time varying. When CR was not reported, as in the case of gemcitabine ± docetaxel, HGRFS was used as a proxy for CR. For population 2, the probability of moving from "Disease-free" to "Persistent/Recurrent NMIBC" was determined from HGRFS survival at 6, 9, 12 months and were time varying. Duration of response Kaplan-Meier curves (for nadofaragene firadenovec and oportuzumab monatox) or reported HGRFS (for gemcitabine ± docetaxel) beyond 12 months and up to 36 months, depending on data availability, were used to estimate the probability of remaining in the "Persistent/Recurrent NMIBC" Markov state for all time periods greater than 12 months. The appropriate form of the equation $P=1-e^{-kt}$ was used to estimate the three-month probability to match the model's cycle length.

One issue that arose from using CR and HGRFS from clinical trials was that the 12-month assessments were conducted differently between trials for nadofaragene firadenovec and oportuzumab monatox. For nadofaragene firadenovec, 12-month assessments for CR and HGRFS were included a biopsy in addition to urine cytology and cystoscopy, whereas for oportuzumab monatox a biopsy was not required at 12 months. In the nadofaragene firadenovec trial, three patients in population 1 and two patients in population 2 were classified as having recurrence at 12 months only as a result of the required biopsy. To better represent these different 12-month outcome assessments, we chose to conduct scenario analyses that 1) estimate the effect of having required biopsies at 12 months in both trials; and 2) estimate the effect of not having required

biopsies at 12 months in both trials. This was done by altering the transition probabilities from the 12-month base case values for both treatments. Although scenario analyses are not usually presented alongside the base case results, we thought that these differences between trials were significant enough that the results should be reported with the base case results. However, sensitivity analyses were not conducted on these scenario analysis results.

Transitions directly from "Disease-free" to "MIBC" were not allowed in the base case of the model; all transitions to the "MIBC" state occurred through the "Persistent/Recurrent NMIBC" state. Progression-free survival was used to estimate transitions from "Persistent/Recurrent NMIBC" to "MIBC." These transitions were calculated by dividing the number of patients at 12 months who had progression (i.e., 1 – progression-free survival) by the cumulative number of patients with NMIBC at 12 months (i.e., 1 – CR or HGRFS), and then adjusting for three-month cycles. Since these estimates were not available for gemcitabine ± docetaxel or the hypothetical treatment, the highest transition probability value from those calculated for nadofaragene firadenovec and oportuzumab monatox was used (i.e., 1.4% for population 1 and 3.0% for population 2). The model inputs for these parameters are shown in the Table 5.4 and 5.5.

For all other model transitions, data were collected from other longer-term epidemiologic studies and clinical trials. Transitions from "Persistent/Recurrent NMIBC" to "Post-Cystectomy" and the transition from "MIBC" to "Post-Cystectomy" were obtained from large retrospective studies.[83,84] Transitions from "MIBC" to "Metastatic Disease" and "Death" were obtained from a large collaborative study combining results from multiple clinical trials.[83,84] Transitions from "Post-Cystectomy" to "Metastatic Disease" were obtained from a large retrospective analysis in 888 patients,[85] while transitions from "Post-Cystectomy" to "Death" were obtained from a retrospective study evaluating 678 patients.[86] Transitions from "Metastatic Disease" to "Death" were obtained from a retrospective study evaluating long-term mortality outcomes in patients treated for locally advanced or metastatic bladder cancer with gemcitabine and cisplatin compared with methotrexate, vinblastine, doxorubicin, and cisplatin.[87] The model inputs for these parameters are shown in Appendix Table E2.

Table 5.4. Key Model Inputs for the CIS ± Ta/T1 Population

Model Input	Nadofaragene Firadenovec	Oportuzumab Monatox	Pembrolizumab	Gemcitabine ± Docetaxel	Hypothetical Treatment	Source
Probability of Complete Response at 3 months	53.4%	40.0%	40.6%	72.0%	0%	Boorjian 2020[82] FerGene, data on file[25] Sesen Bio, data on file[20] Stuart 2019[79] Steinberg 2020[18]
Probability of Transitioning from Complete Response to NMIBC at 6 months	23.6%	30.0%	7.6%	16.7%	N/A	
Probability of Transitioning from Complete Response to NMIBC at 9 months	14.2%	25.0%	25.1%	14.7%	N/A	
Probability of Transitioning from Complete Response to NMIBC at 12 months	30.6%	19.0%	33.1%	6.3%	N/A	
Probability of Transitioning from Complete Response to NMIBC Each Cycle After 12 months	7.3%	11.4%	6.7%	4.5%	N/A	
Probability of Transitioning from NMIBC to MIBC Each Cycle	1.2%	1.4%	1.4%	1.4%	1.4%	

N/A: not applicable, NMIBC: non-muscle invasive bladder cancer

Table 5.5. Key Model Inputs for the High-Grade Ta/T1 Population

Model Input	Nadofaragene Firadenovec	Oportuzumab Monatox	Gemcitabine ± Docetaxel	Hypothetical Treatment	Source
Probability of Complete Response at 3 months	72.9%	71.0%	75.2%	0%	Boorjian 2020[82] FerGene, data on file[25] Sesen Bio, data on file[20] Stuart 2019[79]
Probability of Transitioning from Complete Response to NMIBC at 6 months	14.3%	18.3%	7.4%	N/A	
Probability of Transitioning from Complete Response to NMIBC at 9 months	6.7%	22.4%	14.9%	N/A	
Probability of Transitioning from Complete Response to NMIBC at 12 months	24.9%	6.7%	6.8%	N/A	
Probability of Transitioning from Complete Response to NMIBC Each Cycle After 12 Months	5.8%	7.3%	4.2%	N/A	
Probability of Transitioning from NMIBC to MIBC Each Cycle After 12 Months (Patients with HG Ta/T1)	2.1%	3.0%	3.0%	3.0%	

N/A: not applicable, NMIBC: non-muscle invasive bladder cancer

Discontinuation

Treatment discontinuation was modeled using mean treatment duration. Where mean treatment duration was not available, the median treatment duration was used to estimate the mean treatment duration using an exponential decay function (i.e., e^{-kt}), estimating k, and deriving the mean (which is equal to $1/k$).

Mortality

Mortality was included in the model as described in the Clinical Probabilities/Response to Treatment section above. For patients in the "Initial Treatment," "Disease Free," and "Persistent/Recurrent NMIBC" Markov states, the annual age and gender adjusted mortality probability converted to three months was used for each cycle of the model. For all remaining

Markov states, mortality is higher and was estimated from publications identified through a systematic literature review.[84,86,87]

Utilities

Table 5.6 shows health state utility values used in the model. Where possible, utilities were derived from published literature that estimated bladder cancer-specific values using the EQ-5D. Health state utilities for "Initial Treatment," "Disease Free," "Persistent/Recurrent NMIBC," and "MIBC" were obtained from a study evaluating the EQ-5D in 472 patients with NMIBC.[27] The utility for "Metastatic Disease" was obtained from a study of 270 patients enrolled in the KEYNOTE-045 trial with metastatic urothelial carcinoma.[28] The "Post-Cystectomy" utility value was obtained from a decision model report, where utility was estimated from 25 urologists using the standard gamble method.[29] Table 5.6 shows health state utility values used in the model. Where possible, utilities were derived from published literature that estimated bladder cancer-specific values using the EQ-5D.

As the utility values for "Metastatic Disease" were not obtained from the population under review, and the study evaluating the "Post-Cystectomy" utility queried urologists rather than patients or the general public, the resulting utilities for these two states were higher than what might be expected. Since there were no other credible sources for these utility values, we used these values in the base case and conducted additional one-way sensitivity analyses to evaluate the impact of lower utilities on the model.

Table 5.6. Utility Values for Health States

	Utility Value	Population	Method of Valuation	Source
Initial Treatment	0.86	Patients with NMIBC	EQ-5D	Cox 2019[27]
Disease Free	0.87	Patients with NMIBC	EQ-5D	Cox 2019[27]
NMIBC	0.76	Patients with NMIBC	EQ-5D	Cox 2019[27]
MIBC	0.75	Patients with NMIBC	EQ-5D	Cox 2019[27]
Metastatic Disease	0.70	Patients enrolled in KEYNOTE-045 with metastatic urothelial carcinoma	EQ-5D	Slater 2020[28]
Post-Cystectomy	0.745	Non-patient urologists	Standard Gamble	Kulkarni 2012[29]

NMIBC: non-muscle invasive bladder cancer

Adverse Events

We included only those adverse events likely to result in measurable treatment costs and/or disutility. Grade 1-4 urinary tract infection was a common AE with oportuzumab monatox and pembrolizumab likely to result in treatment for all patients, occurring with a frequency of 12% for each treatment. Therefore, the cost for treating urinary tract infection was factored into the

model. Since AE information for gemcitabine ± docetaxel was obtained from a retrospective study, the severity grade was not reported. Treatment was delayed due to AEs in 15% of patients and discontinued early in 8% of patients. The most common side effects were urinary frequency (22.1%), dysuria (15.6%), and hematuria (10.5%). Since urinary frequency, dysuria, and hematuria were unlikely to accrue significant cost or result in measurable disutility, they were not included in the analysis. Table 5.7 shows the probability, cost, and disutility associated with each included AE, along with cost sources.

Table 5.7. Included Adverse Events

Adverse Event, Treatment	Probability	Cost	Disutility	Sources
Urinary Tract Infection, Oportuzumab Monatox	12%	$167	0	Le 2001[88]
Urinary Tract Infection, Pembrolizumab	12%	$167	0	Le 2001[88]

Economic Inputs

Drug Acquisition Costs

Drug utilization for nadofaragene firadenovec, oportuzumab monatox, pembrolizumab, and gemcitabine ± docetaxel, which were used to determine costs, were obtained from clinical trials.[20,25,89] The mean treatment duration for each was used, along with the recommended dosage and timing of administration, to determine the mean cumulative dose per person. Table 5.8 shows the recommended dosage schedule for these drugs.

At the time of publishing this report, the prices for nadofaragene firadenovec and oportuzumab monatox were not available. We therefore estimated the price of nadofaragene firadenovec using the price of pembrolizumab. The price of oportuzumab monatox was set at $150,000 per year, an estimated price net of rebates that was communicated by Sesen Bio. The price for pembrolizumab was derived using the US Department of Veteran Affairs Office of Procurement Federal Supply Schedule (FSS) prices.[30] The price for gemcitabine ± docetaxel was estimated using WAC, obtained from Micromedex Red Book.[31] Drug cost inputs are shown in Table 5.8.

Table 5.8. Drug Cost Inputs

Intervention	Administration	Unit	WAC or FSS per Unit	Net Price per Dose	Annual Drug Cost‡
Nadofaragene Firadenovec	$3x10^{11}$ vp/mL (75 mL), administered by intravesical instillation every 3 months (total of 4 doses per year).	$3x10^{11}$ vp/mL (75 mL)	$41,084**	$41,084**	$164,337**
Oportuzumab Monatox	30 mg administered by intravesical instillation twice weekly for first 6 weeks, then once weekly for 6 weeks, then every other week thereafter (total of 36 doses in first year).	30 mg	$4,167**	$4,167**	$150,000***
Pembrolizumab	200 mg IV over 30 minutes every 3 weeks or 400 mg IV over 30 minutes every 6 weeks for up to 24 months (total of 17.4 doses per year).	200 mg	$9,455*	$9,455*	$164,337
Gemcitabine ± docetaxel	Gemcitabine 1000 mg and docetaxel 37.5 mg administered weekly for 6 weeks by intravesical instillation	1000 mg and 160 mg	$36.90 and $153.00	$36.90 and $35.86	$437#

FSS: Federal Supply Schedule, WAC: wholesale acquisition cost

*FSS as of August 26, 2020

**The estimated price for nadofaragene firadenovec was assumed to be the annual price of pembrolizumab.

***The estimated price for oportuzumab monatox was provided through communication with Sesen Bio.

‡The annual drug cost includes drug acquisition cost for a full 365 days.

#The annual drug cost for gemcitabine ± docetaxel was estimated for the 6-week course of therapy only.

Administration and Monitoring Costs

The cost of administering nadofaragene firadenovec, oportuzumab monatox, and gemcitabine ± docetaxel was estimated to be $86 per instillation using HCPCS code 51720 (bladder instillation of anticarcinogenic agent). The cost of administering pembrolizumab was estimated to be $143 per infusion using CPT code 96413 (chemotherapy administration, intravenous infusion technique; up to one hour, single or initial substance/drug). Drug administration costs were determined using physician fee schedules from the Centers for Medicare & Medicaid Services.[90] These costs are also presented in Appendix Table E3.

Health Care Utilization Costs

Non-drug health care costs were primarily derived from a study evaluating the cost of surveillance for NMIBC by Mossanen et al.[91] This study utilized a Markov model to determine the average one-year and five-year costs for patients with low, intermediate, and high risk NMIBC. The underlying cost data was obtained from a study of 208 patients treated at MD Anderson Cancer Center. For our analysis, we utilized the cost data for those patients who were at high risk to estimate the costs for being in "Initial Treatment," "Disease Free," and "Persistent/Recurrent NMIBC," and "MIBC." In addition, the short-term cost associated with transitioning to the "Death" Markov state was obtained from Mossanen et al.[91] The cost of "Metastatic Disease" was obtained from an abstract describing the first six months of therapy after the diagnosis of metastatic bladder cancer.[92] For patients having a cystectomy and for the "Post-Cystectomy" Markov state, costs were obtained from two retrospective studies assessing cystectomy admission, costs in the first 90 days, and monthly costs after 90 days.[93,94] All costs were inflated to 2019 US dollars using the Health Care component of the Bureau of Economic Analysis Personal Consumption Expenditures Price Index (PCE), per ICER's Reference Case.

Table 5.9. Health Care Utilization Costs

Cost Description	Cost per Cycle	Source
Initial Treatment	$1,211	Mossanen 2019[91]
Disease Free	$1,211	Mossanen 2019[91]
NMIBC	$1,458	Mossanen 2019[91]
MIBC	$7,027	Mossanen 2019[91]
Cystectomy	$30,625 (one-time)	Leow 2014[93]
Post-Cystectomy	$8,665	Malangone-Monaco 2020[94]
Metastatic Disease	$24,905	Seal 2014[92]
Death	$500	Mossanen 2019[91]

NMIBC: non-muscle invasive bladder cancer

Adverse Event Costs

The costs associated with treating urinary tract infections were estimated using cost data from a decision tree model for uncomplicated urinary tract infection.[88] The cost of treating rash and pruritus were estimated using a physician office visit level 3 billing code (99213), in addition to the cost for one prescription of triamcinolone 0.1% lotion (WAC equal to $18.70) per patient.[90]

Productivity and Other Indirect Costs

Productivity costs for patients and their caregivers were considered for inclusion in the analysis. The impact of NMIBC on patients and their caregivers has been outlined by Mossanen and Gore, and include disruption of personal and professional lives due to treatment, resulting in decreased work productivity and earning potential.[95] Requiring a Foley catheter for those who elect to

undergo TURBT can also impact the ability work for some patients. For those who undergo cystectomy, there may be anxiety and fear inadequately captured by utility measures.[96] Caregiver burden, anxiety, fear, and other factors may be significant for patients with metastatic disease.

Although considered for inclusion in the analysis, there have been few studies that evaluate the impact of these factors on indirect costs. Those few studies have been conducted in patients undergoing cystectomy or who are post-cystectomy and have shown that while pain and anxiety may be significant, caregiver burden is low.[96] Unfortunately, no studies were identified that quantified indirect costs for patients other than those had undergone cystectomy. Therefore, we were unable to include an analysis evaluating a modified societal perspective incorporating these indirect costs.

Sensitivity Analyses

We ran one-way sensitivity analyses to identify the key drivers of model outcomes, using available measures of parameter uncertainty (i.e., standard errors) or reasonable ranges for each input described in the model inputs section above. The utilities derived from the literature associated with cystectomy[29] and metastatic disease[28] were obtained from different sources than those for all other utilities[27] and appeared to be high relative to these other utilities. We conducted one-way sensitivity analyses on each of these variables to estimate the impact of potentially more plausible utilities on the model results. In a separate analysis, we varied the proportion of patients with MIBC who chose to undergo cystectomy from 0% to 100% to determine the impact on threshold prices for nadofaragene firadenovec and oportuzumab monatox. We ran one-way sensitivity analyses to identify the key drivers of model outcomes, using available measures of parameter uncertainty (i.e., standard errors) or reasonable ranges for each input described in the model inputs section above. The utilities derived from the literature associated with cystectomy[29] and metastatic disease[28] were obtained from different sources than those for all other utilities[27] and appeared to be high relative to these other utilities. We conducted one-way sensitivity analyses on each of these variables to estimate the impact of potentially more plausible utilities on the model results. In a separate analysis, we varied the proportion of patients with MIBC who chose to undergo cystectomy from 0% to 100% to determine the impact on threshold prices for nadofaragene firadenovec and oportuzumab monatox.

Probabilistic sensitivity analyses were also performed by jointly varying all the model parameters over 1,000 simulations, then calculating 95% credible range estimates for each model outcome based on the results. For the parameters of the probabilistic sensitivity analyses, we used beta distributions for probabilities, gamma distributions for costs, and beta distributions for utilities. Additionally, we performed a threshold analysis by systematically altering the price of nadofaragene firadenovec and oportuzumab monatox to estimate the maximum prices that would correspond to given willingness-to-pay (WTP) thresholds.

Scenario Analyses

Effect of Biopsy on Cost-Effectiveness Outcomes

As described above, the clinical trials for nadofaragene firadenovec and oportuzumab monatox evaluated 12-month CR and HGRFS differently. The trial for nadofaragene firadenovec required a biopsy, whereas the trial for oportuzumab monatox did not. As a result, three patients in population 1 and two patients in population 2 were classified as having recurrence at 12 months when the biopsy results were included, compared to when biopsy results were not included. We conducted a sensitivity analysis to evaluate the following outcomes:

1. We calculated an optimistic scenario by assuming the recurrences identified by biopsy alone at the 12-month CR and HGRFS outcomes did not happen in the nadofaragene firadenovec study. No changes were made to oportuzumab monatox.

2. We calculated a conservative scenario by assuming the recurrences identified by biopsy alone at the 12-month CR and HGRFS outcomes did happen in the nadofaragene firadenovec study. These changes were also applied to oportuzumab monatox, assuming that three additional patients in population 1 and two additional patients in population 2 would have been identified had a biopsy been conducted.

Due to the potential impact of these differences in study design on the incremental cost-effectiveness of nadofaragene firadenovec and oportuzumab monatox, we chose to present these results alongside the base case results. These results were also used to calculate a wider value-based pricing reported in section 7 of this report.

Threshold Analyses

To assess the impact of nadofaragene firadenovec and oportuzumab monatox pricing on incremental cost effectiveness, we varied the prices of these drugs to determine the threshold prices required to obtain ICERs of $50,000 per QALY gained to $150,000 per QALY gained.

Model Validation

We used several approaches to validate the model. First, we provided preliminary methods and results to manufacturers, patient groups, and clinical experts. Based on feedback from these groups, we refined data inputs used in the model. Second, we varied model input parameters to evaluate face validity of changes in results. We performed model verification for model calculations using internal reviewers. Finally, we compared results to other cost-effectiveness models in this therapy area.

5.3 Results

Base-Case Results

Given the "I" rating for the comparison of nadofaragene firadenovec and oportuzumab monatox with pembrolizumab and gemcitabine ± docetaxel, the incremental cost effectiveness of nadofaragene firadenovec and oportuzumab monatox compared with pembrolizumab and gemcitabine ± docetaxel were not calculated. However, we did calculate the incremental cost effectiveness of pembrolizumab and gemcitabine ± docetaxel compared with the hypothetical treatment. When interpreting these results, it is important to consider that BCG-unresponsive NMIBC involves a heterogeneous population and that trials may have enrolled patients with differing characteristics that might affect study outcomes. In addition, the retrospective study evaluating gemcitabine ± docetaxel delivered care and documented outcomes different from the prospective noncomparative clinical trials of nadofaragene firadenovec, oportuzumab monatox, and pembrolizumab, introducing further uncertainty as to the comparability of study outcomes for gemcitabine ± docetaxel to those for the newer treatments. The lack of a placebo control or active comparator group compounds the difficulty in interpreting these results.

Since the prices for nadofaragene firadenovec were not available at the time of publishing this report, we used prices in the model that were based on the annual price of pembrolizumab, taking into account differences in dosing frequency. The estimated price for oportuzumab monatox was provided by Sesen Bio as approximately $150,000 per year net of discounts and rebates. The total discounted lifetime costs, QALYs, evLYGs, LYGs, and time in progression-free health state are shown for nadofaragene firadenovec, oportuzumab monatox, gemcitabine ± docetaxel, and the hypothetical treatment in Table 5.10 for the CIS ± HG Ta/T1 population and Table 5.11 for the HG Ta/T1 alone population. The results for pembrolizumab, evaluated in the CIS ± HG Ta/T1 population only, are shown in Table 5.10. Undiscounted base-case results are presented in Appendix Tables E4 and E5.

Table 5.10. Results for the Base Case for Nadofaragene Firadenovec and Oportuzumab Monatox Compared to Pembrolizumab and the Hypothetical Treatment in Patients with CIS ± High Grade Ta/T1

Treatment	Drug Cost (per Year)	Total Cost	QALYs	evLYGs	Life Years	Time in Progression-Free State (Years)
Results Based on Prospective Studies of Instilled Therapies						
Nadofaragene Firadenovec	$164,000*	$308,000	5.17	5.26	6.71	3.99
Oportuzumab Monatox	$150,000**	$310,000	4.69	4.73	6.16	3.23
Results Based on Prospective Studies of Systemic Therapy						
Pembrolizumab	$164,000	$265,000	5.04	5.12	6.57	3.81
Results Based on Retrospective Studies of Instilled Therapies						
Gemcitabine ± Docetaxel	$440	$172,000	5.88	6.00	7.42	4.82
Results Based on Hypothetical Treatment						
Hypothetical Treatment	$0	$189,000	4.38	4.38	5.83	2.80

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

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

**Price for oportuzumab monatox was provided by Sesen Bio as net discounts and rebates

Table 5.11. Results for the Base Case for Nadofaragene Firadenovec and Oportuzumab Monatox Compared to the Hypothetical Treatment in Patients with High Grade Ta/T1 Alone

Treatment	Drug Cost (per Year)	Total Cost	QALYs	evLYGs	Life Years	Time in Progression-Free State (Years)
Results Based on Prospective Studies of Instilled Therapies						
Nadofaragene Firadenovec	$93,000*	$302,000	5.52	5.64	7.03	4.43
Oportuzumab Monatox	$150,000**	$302,000	5.23	5.32	6.70	3.96
Results Based on Retrospective Studies of Instilled Therapies						
Gemcitabine ± Docetaxel	$440	$165,000	5.83	5.95	7.32	4.85
Results Based on Hypothetical Treatment						
Hypothetical Treatment	$0	$190,000	4.31	4.31	5.75	2.69

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

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

**Price for oportuzumab monatox was provided by Sesen Bio as net discounts and rebates

The cost per QALY gained, cost per evLYG, and cost per year in a progression-free state for nadofaragene firadenovec, oportuzumab monatox, pembrolizumab, and gemcitabine ± docetaxel

compared with the hypothetical treatment (with the complete response probability set to 0%), are shown in Table 5.12 (for the CIS ± Ta/T1 subgroup) and Table 5.13 (for the HG Ta/T1 subgroup).

Table 5.12. 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 based on annual price of pembrolizumab

Table 5.13. 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 based on annual price of pembrolizumab

In scenario analyses, we evaluated the impact of determining the 1) inclusion and 2) exclusion of patients with recurrence of their bladder cancer assessed via biopsy alone for nadofaragene firadenovec and oportuzumab monatox. Those results are shown in the tables 5.14 and 5.15 below.

Table 5.14. Scenario Analysis of the Incremental Cost-Effectiveness Ratios for Nadofaragene Firadenovec and Oportuzumab Monatox in Patients with CIS ± Ta/T1 Accounting for Recurrence Being Assessed via Biopsy Alone

Treatment	Comparator	Base Case	Inclusion of Patients Assessed via Biopsy	Exclusion of Patients Assessed via Biopsy
Nadofaragene Firadenovec*	Hypothetical Treatment	$151,000	$151,000	$142,000
Oportuzumab Monatox	Hypothetical Treatment	$382,000	$435,000	$382,000

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

Table 5.15. Scenario Analysis of the Incremental Cost-Effectiveness Ratios for Nadofaragene Firadenovec and Oportuzumab Monatox in Patients with High Grade Ta/T1 Accounting for Recurrence Being Assessed via Biopsy Alone

Treatment	Comparator	Base Case	Inclusion of Patients Assessed via Biopsy	Exclusion of Patients Assessed via Biopsy
Nadofaragene Firadenovec*	Hypothetical Treatment	$93,000	$93,000	$86,000
Oportuzumab Monatox	Hypothetical Treatment	$123,000	$136,000	$123,000

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

In a sensitivity analysis, we varied the effectiveness of the hypothetical treatment from a CR of 0% to 40% in population 1 and 60% in population 2. As the effectiveness of the hypothetical treatment increased, the incremental cost-effectiveness ratios of both nadofaragene firadenovec and oportuzumab monatox also increased. The complete results of these analyses are shown in Tables 5.16 and 5.17.

Table 5.16. Impact of Varying the Effectiveness of the Hypothetical Treatment on the Incremental Cost-Effectiveness Ratios for Nadofaragene Firadenovec and Oportuzumab Monatox Compared to Hypothetical Treatment in Patients with CIS ± Ta/T1

Effectiveness of Hypothetical Treatment (% with Complete Response at 3 Months)	Nadofaragene Firadenovec* Cost per QALY Gained	Oportuzumab Monatox Cost per QALY Gained
0% (Base Case)	$151,000	$382,000
10%	$153,000	$394,000
20%	$155,000	$407,000
30%	$160,000	$444,000

QALY: quality-adjusted life year

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

Table 5.17. Impact of Varying the Effectiveness of the Hypothetical Treatment on the Incremental Cost-Effectiveness Ratios for Nadofaragene Firadenovec and Oportuzumab Monatox Compared to Hypothetical Treatment in Patients with High Grade Ta/T1

Effectiveness of Hypothetical Treatment (% with Complete Response at 3 Months)	Nadofaragene Firadenovec* Cost per QALY Gained	Oportuzumab Monatox Cost per QALY Gained
0% (Base Case)	$93,000	$123,000
10%	$94,000	$125,000
20%	$98,000	$131,000
30%	$107,000	$147,000
40%	$125,000	$182,000
50%	$157,000	$257,000
60%	$225,000	$493,000

QALY: quality-adjusted life year

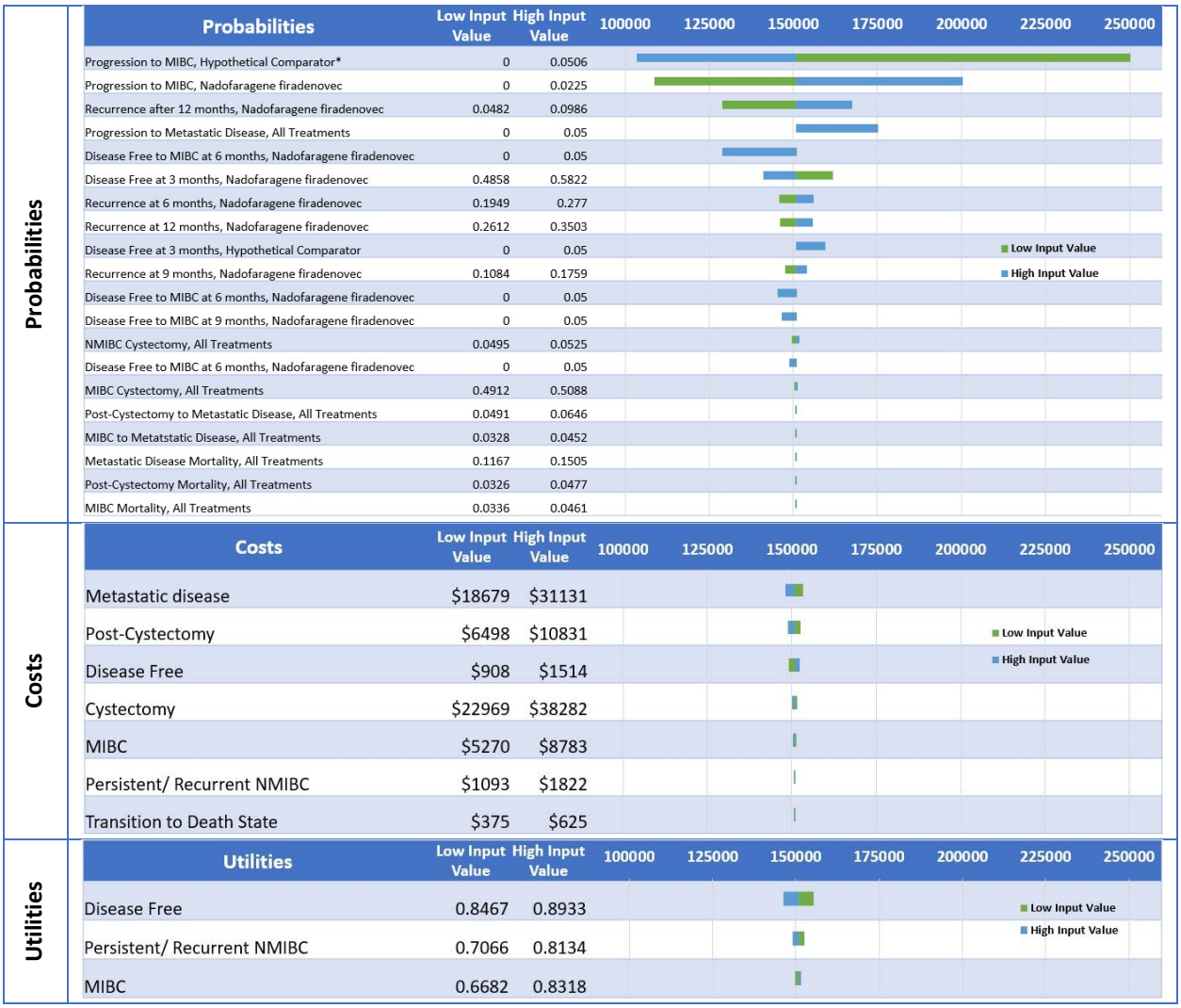
*Price for nadofaragene firadenovec was based on annual price of pembrolizumab

Sensitivity Analysis Results

To demonstrate effects of uncertainty on both costs and health outcomes, we varied input parameters using available measures of parameter uncertainty (i.e., standard errors) or reasonable ranges to evaluate changes in cost per additional QALY for nadofaragene firadenovec and oportuzumab monatox compared to the hypothetical treatment in both subgroups. The primary drivers of model uncertainty for population 1 (CIS) were the transition probabilities of disease progression (i.e., moving from NMIBC to MIBC), having recurrence, especially after 12 months (i.e., moving from Disease Free to NMIBC after 12 months), and achieving CR (treatments and the hypothetical treatment). Although the base case restricted direct movement from Disease Free to MIBC, when subjected to sensitivity analyses this transition probability was also an important contributor to the analysis results. Cost inputs had minimal impact on the cost-effectiveness results. The utility of being in the Disease-Free state also had some impact on the model results. Results were similar for patients in population 2 (HG Ta/T1), although the contributions of each

variable differed slightly from population 1. The full one-way sensitivity analyses are shown in Figures 5.2-5.5.

Figure 5.2. Tornado Diagrams for One-Way Sensitivity Analyses of Nadofaragene Firadenovec versus Hypothetical Treatment in Patients with CIS ± Ta/T1



Price for nadofaragene firadenovec was based on annual price of pembrolizumab

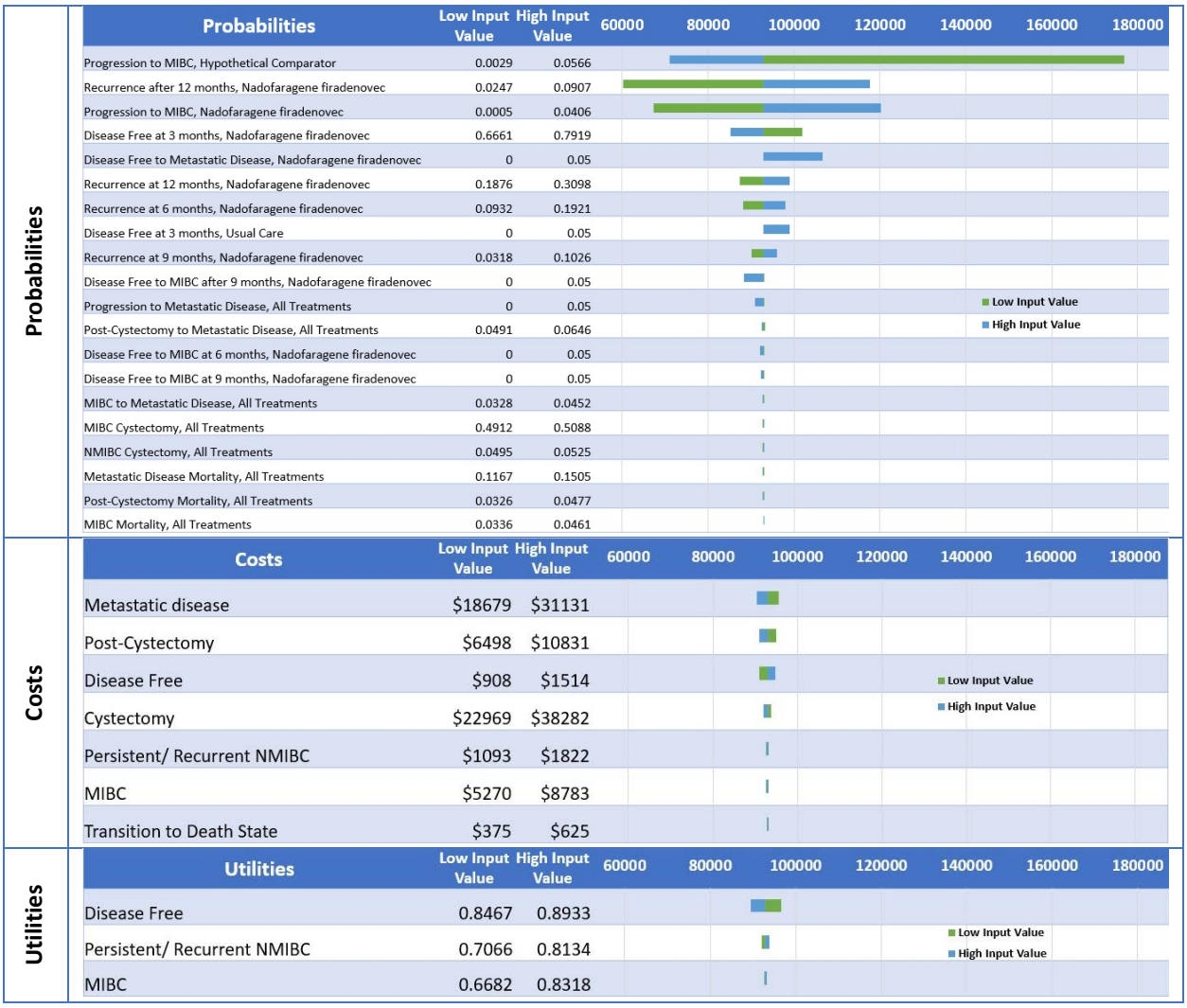
*Incremental cost-effectiveness ratio range: $103,553 to $516,635

Figure 5.3. Tornado Diagrams for One-Way Sensitivity Analyses of Oportuzumab Monatox versus Hypothetical Treatment in Patients with CIS ± Ta/T1

*Incremental cost-effectiveness ratio range: $190,254 to $1,225,835

#Incremental cost-effectiveness ratio range: $183,146 to $569,992

Figure 5.4. Tornado Diagrams for One-Way Sensitivity Analyses of Nadofaragene Firadenovec versus Hypothetical Treatment in Patients with High Grade Ta/T1



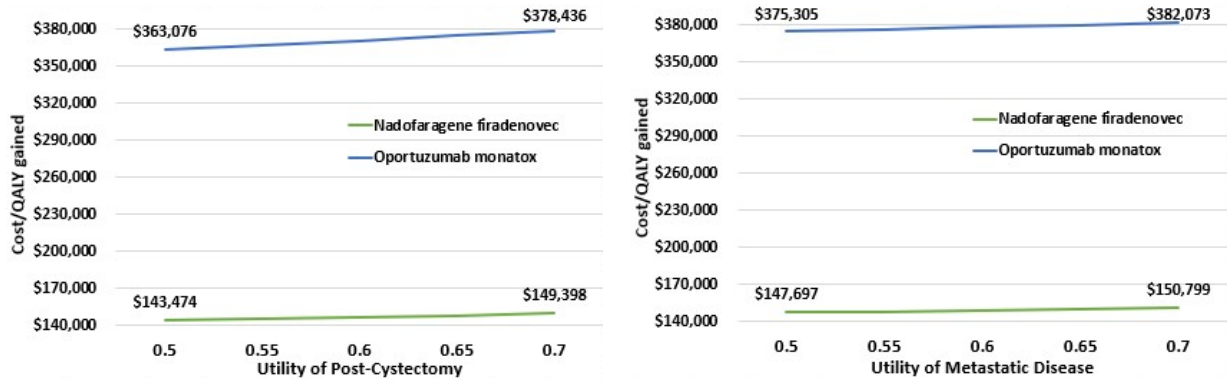
Price for nadofaragene firadenovec was based on annual price of pembrolizumab

Figure 5.5. Tornado Diagrams for One-Way Sensitivity Analyses of Oportuzumab Monatox versus Hypothetical Treatment in Patients with High Grade Ta/T1

*Incremental cost-effectiveness ratio range: $87,765 to $312,534

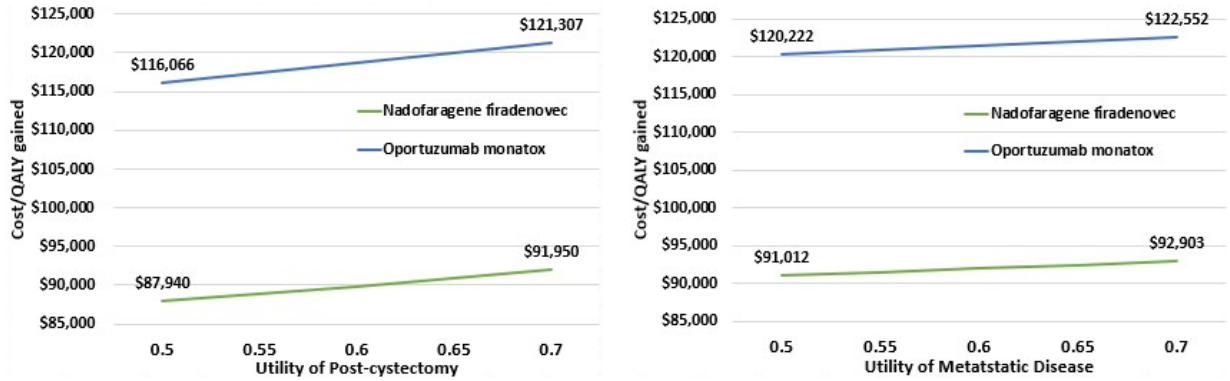
We also conducted specific one-way sensitivity analyses evaluating the utilities associated with the "Post-Cystectomy" and "Metastatic Disease" Markov states. These analyses are shown in Figures 5.6 and 5.7. Varying these utility estimates had minimal impact on incremental cost-effectiveness ratios.

Figure 5.6. One-Way Sensitivity Analysis Varying Utility of Post-Cystectomy and Metastatic Disease in Patients with CIS ± Ta/T1*



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

Figure 5.7. One-Way Sensitivity Analysis Varying Utility of Post-Cystectomy and Metastatic Disease in Patients with HG Ta/T1*



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

Altering the probability of patients with MIBC undergoing cystectomy, from the base-case value of 50% per cycle, to between 0% and 100% per cycle, also had minimal impact on the incremental cost-effectiveness ratio. The resulting changes to the incremental cost-effectiveness ratio were within ± $2,000 per QALY gained for each therapy.

The probabilistic sensitivity analysis shows the overall variability in the model for nadofaragene firadenovec and oportuzumab monatox, compared with the hypothetical treatment for the CIS ± Ta/T1 and HG Ta/T1 populations. Results for nadofaragene firadenovec and oportuzumab monatox were generally above a cost-effectiveness threshold of $150,000 per QALY gained in the CIS ± Ta/T1 subgroup (44.8% and 12.2% at $150,000 per QALY gained, respectively) while those in the HG Ta/T1

subgroup were generally below $150,000 per QALY (82.1% and 65.7% at $150,000 per QALY gained, respectively). The full results are shown in Tables 5.18 and 5.19.

Table 5.18. Probabilistic Sensitivity Analysis Results: Nadofaragene Firadenovec and Oportuzumab Monatox Compared to Hypothetical Treatment in Patients with CIS ± Ta/T1

	Cost Effective at $50,000 per QALY	Cost Effective at $100,000 per QALY	Cost Effective at $150,000 per QALY	Cost Effective at $200,000 per QALY	Cost Effective at $250,000 per QALY
Nadofaragene Firadenovec	0.2%	15.7%	44.8%	63%	74.3%
Oportuzumab Monatox	0%	1.5%	12.2%	22.2%	30.7%

QALY: quality-adjusted life year

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

Table 5.19. Probabilistic Sensitivity Analysis Results: Nadofaragene Firadenovec and Oportuzumab Monatox Compared to Hypothetical Treatment in Patients with High Grade Ta/T1

	Cost Effective at $50,000 per QALY	Cost Effective at $100,000 per QALY	Cost Effective at $150,000 per QALY	Cost Effective at $200,000 per QALY	Cost Effective at $250,000 per QALY
Nadofaragene Firadenovec	8.3%	60.5%	82.1%	89.9%	93.8%
Oportuzumab Monatox	3.7%	41.2%	65.7%	78.8%	84.4%

QALY: quality-adjusted life year

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

Scenario Analyses Results

Threshold Analyses Results

Tables 5.20 and 5.21 show the annual prices required to meet cost-effectiveness thresholds of $50,000, $100,000, and $150,000 per QALY gained using the base case inputs for all other variables except drug price.

Table 5.20. Threshold Analysis Results in Patients with CIS ± Ta/T1

	WAC per Unit	Net Price per Unit	Annual Price to Achieve $50,000 per QALY	Annual Price to Achieve $100,000 per QALY	Annual Price to Achieve $150,000 per QALY
Nadofaragene Firadenovec	N/A	N/A	$64,500	$114,000	$163,500
Oportuzumab Monatox	N/A	N/A	$21,700	$41,000	$60,400

N/A: not available, WAC: wholesale acquisition cost

Table 5.21. Threshold Analysis Results in Patients with High Grade Ta/T1

	WAC per Unit	Net Price per Unit	Annual Price to Achieve $50,000 per QALY	Annual Price to Achieve $100,000 per QALY	Annual Price to Achieve $150,000 per QALY
Nadofaragene Firadenovec	N/A	N/A	$99,400	$175,000	$250,700
Oportuzumab Monatox	N/A	N/A	$69,300	$124,900	$180,500

N/A: not available, WAC: wholesale acquisition cost

Model Validation

Model validation followed standard practices in the field. We tested all mathematical functions in the model to ensure they were consistent with the report (and supplemental Appendix materials). We also conducted sensitivity analyses with null input values to ensure the model was producing findings consistent with expectations. Further, independent modelers tested the mathematical functions in the model as well as the specific inputs and corresponding outputs.

Model validation was also conducted in terms of comparisons to other model findings. We searched the literature to identify models that were similar to our analysis, with comparable populations, settings, perspective, and treatments.

Prior Economic Models

In order to develop a comprehensive model and identify potential model inputs, we reviewed several prior models for patients with bladder cancer. These models typically focused on diagnosis,[97,98] surveillance,[91,99,100] non-drug treatment,[101-103,29,104,105] and drug treatment.[101-103] All of the studies utilized a Markov or semi-Markov model, except for one evaluating a diagnostic approach,[98] which utilized a hybrid simple decision tree and Markov. Of these studies, two included a patient population similar to the one evaluated in our analysis.[29,102]

Cycle lengths in these analyses varied from three months to one year. Time horizons varied between two years[99] and lifetime.[29,100] Of those studies evaluating drug treatments, one study

evaluated pembrolizumab as second-line treatment of advanced bladder cancer, a different population;[101] one study evaluated low-dose BCG in patients with intermediate and high-risk NMIBC;[103] and one study evaluated radical cystectomy compared with mitomycin in BCG-refractory patients.[102] Two studies evaluated BCG-refractory high-risk populations similar to ours, one comparing cystectomy to no cystectomy[29] and one evaluating radical cystectomy compared with mitomycin.[102] Cycle lengths in these analyses varied from three months to one year. Time horizons varied between two years[99] and lifetime.[29,100] Of those studies evaluating drug treatments, one study evaluated pembrolizumab as second-line treatment of advanced bladder cancer, a different population;[101] one study evaluated low-dose BCG in patients with intermediate and high-risk NMIBC;[103] and one study evaluated radical cystectomy compared with mitomycin in BCG-refractory patients.[102] Two studies evaluated BCG-refractory high-risk populations similar to ours, one comparing cystectomy to no cystectomy[29] and one evaluating radical cystectomy compared with mitomycin.[102]

Compared with our final model structure, most models omitted important Markov states. In particular, most models omitted MIBC and metastatic cancer states, either evaluating a shorter time horizon or combining these states into a single "progression" state. Those models that most resembled our model evaluated diagnostic and surveillance approaches.[91,97,100] One of the models was particularly helpful in providing cost inputs for our model.[91] Another model was used to identify estimates for otherwise unavailable utilities for cystectomy and the post-cystectomy Markov states, drawn from a survey of 25 urologists.[29]

One of the models reviewed potentially competing treatments for nadofaragene firadenovec and oportuzumab monatox in a similar population.[102] This model evaluated patients receiving conservative therapy (mitomycin) or cystectomy in BCG-refractory patients. Since cystectomy was considered as a comparator, it was not included as a Markov state in the mitomycin treatment arm. Mitomycin resulted in an 17.8% overall mortality at 5 years compared with 23.8% for cystectomy. Five-year cost for mitomycin was $68,517 and for cystectomy was $64,675. The utilities of these treatments were not considered in this model. By comparison, the five-year mortality and five-year costs in our model were 35% and averaged approximately $91,000 (excluding treatment costs), respectively, for the CIS ± Ta/T1 subgroup and 28% and approximately $79,000 for the HG Ta/T1 subgroup. While the costs between these two analyses are comparable when adjusted for inflation, the higher mortality rates in our model may be partly explained by the starting age (69 in Patel et al. vs. 72 in our study), different model structure and inputs, and heterogeneity in the included patient population and included studies representing that population.

Heterogeneity and Subgroups

There is considerable heterogeneity among patients with bladder cancer. Our analysis focused on BCG-unresponsive high-risk NMIBC patients. However, given the considerable differences in pathology even among this group of patients, we decided to evaluate two separate subgroups,

those with CIS ± Ta/T1 and those with HG Ta/T1. Unfortunately, many studies evaluating BCG-unresponsive high-risk patients do not differentiate between these subgroups. In addition, few studies evaluating MIBC and metastatic bladder cancer outcomes include information regarding timing of cancer diagnosis, site and pathology of the original tumor, courses of treatment received, and other potentially prognostic information. Therefore, many of the model inputs were for a pooled population who may or may not accurately represent the intended patient population in this model.

Uncertainties and Controversies

In developing this model, there were many uncertainties regarding treatment of patients with BCG-unresponsive high-risk NMIBC. Importantly, none of the included studies involved control subjects. As a result, the comparative effectiveness of treatments is difficult to evaluate given the heterogeneity that exists among patients with high-risk NMIBC. Also, few studies have evaluated patient outcomes beyond one year, making long-term extrapolation of important outcomes difficult. Comparison of these agents to each other and to other potential comparators should therefore carefully consider this potential uncertainty. As a result, we chose to primarily compare nadofaragene firadenovec and oportuzumab monatox to a hypothetical treatment comparator, which could subsequently be substituted with estimates of the effectiveness of potential real comparators, to estimate the incremental cost effectiveness of these new treatments. It should be noted that in the base case, the effectiveness of the hypothetical treatment comparator was set to a CR of 0% at three months. We were informed by clinical experts that some patients receiving no treatment would still be likely to have a CR at three months, due to receiving TURBT for those in population 2 and variability in diagnostic staging procedures. Therefore, the resulting base case incremental cost-effectiveness ratio estimates and sensitivity analyses are likely to be biased in favor of the new treatments.

In the model, we chose to use the reported numbers of patients who had recurrence or were censored for observations (i.e., patients completely discontinued participation in the study), assuming the worst outcome for patients who were censored, between 0 and 12 months. Although few patients were censored during this time period, those who were censored left the trial primarily because of adverse events to treatment and received few doses of the study drugs. This resulted in a conservative estimate of the incremental cost-effectiveness of nadofaragene firadenovec and oportuzumab monatox compared with the hypothetical treatment. Manufacturers would have preferred the use of Kaplan-Meier estimates for disease recurrence or treatment duration of response. However, Kaplan-Meier estimates assume that the reason for censoring is not related to the treatment or response. We believed that this assumption was not justifiable and the use of Kaplan-Meier estimates for disease recurrence would have been biased in favor of treatments.

The models' results were highly dependent on the effect of treatment on preventing recurrence after 12 months. Given that censoring beyond 12 months was more likely to be random, we did use the mean modeled Kaplan-Meier estimates from 12 to 24 months, or longer where data was available, to calculate transition probabilities after 12 months. However, clinical trials of nadofaragene firadenovec and oportuzumab monatox were small and censoring beyond 12 months was extremely high, with a very small number of observations at 24 months and large confidence intervals around these point estimates. As a result, the long-term cost-effectiveness estimates are very unstable, as shown in the tornado diagrams. In order to improve these estimates of long-term cost effectiveness, future studies should assess the duration of response beyond 12 months in larger numbers of patients.

The mean treatment duration for all three treatments (nadofaragene firadenovec, oportuzumab monatox, and pembrolizumab) were similar and were less than one year. Treatment duration may be shorter than anticipated for a variety of reasons, including lack of continued response to treatment, AEs, choosing to undergo cystectomy, and patient willingness to undergo continued treatment. Also, the average age of patients treated for BCG-unresponsive high-risk NMIBC was 72 years, which may factor into treatment decisions, especially with treatments that have bothersome adverse effects. This relatively short treatment duration may result in lower drug costs and poorer treatment outcomes than might be expected in patients able to continue treatment for the full two-year treatment duration. The cost effectiveness of longer treatment durations could not be modeled because of the unknown impact of longer durations on high-grade recurrence free survival and progression-free survival.

There were limited data on the direct costs associated with the NMIBC health state and long-term complications of NMIBC. We estimated direct costs from a study evaluating episodic health care costs and a subsequent Markov model that extrapolated episodic health care costs to time intervals more usable in the model.[91,106] However, data from Avritsher et al. were collected at a single site with a relatively small number of observations (306 consecutive patients) between January 1, 1991 and December 31, 1999. Despite inflation of these costs, the cost of care may be substantially different nationally and 20-30 years later. One recent abstract had a more nationally representative sample using SEER Medicaid data that was considered for inclusion in the model.[107] However, upon further review it was determined that comparisons between patients with and without progression included costs not specific to bladder cancer, groups were significantly different at baseline, costs associated with cystectomy were included for both groups, and, most importantly, costs for those with progression included metastatic disease. Since it was not possible to remove important confounders or differentiate the costs of having MIBC, cystectomy, and metastatic disease from each other, it was determined that the results of this study could not be used to accurately estimate the costs of MIBC, cystectomy, or metastatic disease in the model.

The outcomes for gemcitabine ± docetaxel were drawn from a retrospective analysis. It is likely that the determination of HGRFS in the real-world setting in which this study was conducted differs

from assessments in clinical trials of nadofaragene firadenovec, oportuzumab monatox, and pembrolizumab. A delay in determining progression, which was likely in this retrospective analysis, may have had a large impact on the resulting cost-effectiveness of this treatment option. However, gemcitabine ± docetaxel remains a potentially effective and relatively inexpensive treatment option.

Limitations

There were several limitations in this analysis, many of which have already been outlined above. The most critical limitations were the need to impose assumptions that may not represent reality (e.g., restricting patients with metastatic disease from moving to the post-cystectomy state), lack of randomized, controlled clinical trials evaluating treatment efficacy, and poor long-term data on progression of NMIBC from epidemiologic studies, especially in patients whose cancer did not respond to BCG. Data estimating the utility of post-cystectomy patients and those with metastatic disease were lacking. We substituted data obtained from non-patients (post-cystectomy) or from similar conditions (metastatic disease) to estimate the impact of these conditions on utility and conducted extensive sensitivity analyses to address this limitation. Also, there was very limited information in the public domain regarding timing, severity, duration, and management of treatment-related AEs.

Importantly, final prices for these therapies have not been released by the manufacturers, precluding final determination of their cost effectiveness.

Finally, we were unable to identify studies that could assist us with determining indirect costs associated with high-grade NMIBC. While it has been suggested that these costs may be considerable, there were no valid comprehensive estimates for the impact of bladder cancer on caregiver and patient time, factors not covered from the health care system perspective but relevant to patients. Given the age of patients with bladder cancer, many may not be working at the time of diagnosis and treatment. However, for those who do work, the impact on absenteeism and presenteeism could be substantial.

5.4 Summary and Comment

Final pricing is not yet available for nadofaragene firadenovec and oportuzumab monatox, making it difficult to determine whether these treatments for BCG-unresponsive high-risk NMIBC will be cost effective. Even if prices were known, estimates were highly dependent on the probability of having recurrence after 12 months and somewhat dependent on the efficacy of a hypothetical comparator treatment. Unfortunately, the clinical trials in which these treatments were evaluated were small and did not have an active or placebo comparator. Therefore, these cost-effectiveness estimates are unstable due to the small number of patients evaluated beyond 12 months and may be higher

because of our need to use a hypothetical comparator with 0% effectiveness in the model to generate cost-effectiveness ratios.

As expected, when the effectiveness of the comparator was increased, the ICERs for both treatments increased. As a result, determining an appropriate and fair health-benefit based price for this heterogeneous group of patients will be difficult, made even more so by not having evidence on potential comparators. Sensitivity analyses indicated that the threshold price is primarily dependent on the relative effectiveness in achieving a CR and in the durability of that response.

In patients with CIS ± Ta/T1, pembrolizumab resulted in important QALY gains and appeared to be cost effective when compared with the hypothetical treatment comparator. Gemcitabine ± docetaxel was more effective and less costly than the hypothetical treatment comparator, resulting in it dominating the hypothetical treatment. Gemcitabine ± docetaxel appears to be a cost-effective, if not dominant, option for patients with BCG-unresponsive NMIBC.

6. Potential Other Benefits and Contextual Considerations

Our reviews seek to provide information on potential other benefits offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that would not have been considered as part of the evidence on comparative clinical effectiveness. We also recognize that there may be broader contextual issues related to the severity of the condition, whether other treatments are available, and ethical, legal, or other societal priorities that influence the relative value of illnesses and interventions. These general elements are listed in Table 6.1, and the subsequent text provides detail about the elements that are applicable to the comparison of nadofaragene firadenovec and oportuzumab monatox to pembrolizumab and gemcitabine with or without docetaxel. We sought input from stakeholders, including individual patients, patient advocacy organizations, clinicians, and manufacturers, to inform the contents of this section.

Each ICER review culminates in a public meeting of an independent voting Council of clinicians, patients, and health services researchers. As part of their deliberations, Council members will judge whether a treatment may substantially impact the considerations listed in Table 6.1. The presence of substantial other benefits or contextual considerations may shift a council member's vote on an intervention's long-term value for money to a different category than would be indicated by the clinical evidence and cost-effectiveness analyses alone. For example, a council member may initially consider a therapy with an incremental cost-effectiveness ratio of $150,000 per QALY to represent low long-term value for money. However, the Council member may vote for a higher value category if they consider the treatment to bring substantial other benefits or contextual considerations. Conversely, disadvantages associated with a treatment may lead a Council member to vote for a lower value category. A Council member may also determine that there are no other benefits or contextual considerations substantial enough to shift their vote. All factors that are considered in the voting process are outlined in ICER's value assessment framework. The content of these deliberations is described in the last chapter of ICER's Final Evidence Report, which is released after the public meeting.

This section, as well as the Council's deliberation, provides stakeholders with information to inform their decisions on a range of issues, including shared decision making between patients and clinicians, coverage policy development, and pricing negotiations.

Table 6.1. Potential Other Benefits or Contextual Considerations (Not Specific to Any Disease or Therapy)

Likert Scale of Potential Other Benefits and Contextual Considerations		
1 (Suggests Lower Value)	**2 (Intermediate)**	**3 (Suggests Higher Value)**
Uncertainty or overly favorable model assumptions creates significant risk that base-case cost-effectiveness estimates are too optimistic.		Uncertainty or overly unfavorable model assumptions creates significant risk that base-case cost-effectiveness estimates are too pessimistic.
Very similar mechanism of action to that of other active treatments.		New mechanism of action compared to that of other active treatments.
Delivery mechanism or relative complexity of regimen likely to lead to much lower real-world adherence and worse outcomes relative to an active comparator than estimated from clinical trials.		Delivery mechanism or relative simplicity of regimen likely to result in much higher real-world adherence and better outcomes relative to an active comparator than estimated from clinical trials.
This intervention could reduce or preclude the potential effectiveness of future treatments.		This intervention offers the potential to increase access to future treatment that may be approved over the course of a patient's lifetime.
The intervention offers no special advantages to patients by virtue of presenting an option with a notably different balance or timing of risks and benefits.		The intervention offers special advantages to patients by virtue of presenting an option with a notably different balance or timing of risks and benefits.
This intervention will not differentially benefit a historically disadvantaged or underserved community.		This intervention will differentially benefit a historically disadvantaged or underserved community.
Small health loss without this treatment as measured by absolute QALY shortfall.		Substantial health loss without this treatment as measured by absolute QALY shortfall.
Small health loss without this treatment as measured by proportional QALY shortfall.		Substantial health loss without this treatment as measured by proportional QALY shortfall.
Will not significantly reduce the negative impact of the condition on family and caregivers vs. the comparator.		Will significantly reduce the negative impact of the condition on family and caregivers vs. the comparator.
Will not have a significant impact on improving return to work and/or overall productivity vs. the comparator.		Will have a significant impact on improving return to work and/or overall productivity vs. the comparator.
Other		Other

Nadofaragene Firadenovec

The mechanism of action of nadofaragene firadenovec is new for the treatment of patients with BCG-unresponsive NMIBC. Given the single-arm study that evaluated it, how it compares to oportuzumab monatox, pembrolizumab, and gemcitabine with or without docetaxel is uncertain. The CR rates seen suggest that it will help some patients with this disease, but that most patients will end up with disease recurrence or progression over time. Administration of nadofaragene firadenovec is through instillation into the bladder, similar to other medications given for NMIBC.

Nadofaragene firadenovec is dosed much less frequently, every 3 months, than other instillation medications including oportuzumab monatox, an advantage during the COVID-19 pandemic where minimizing office visits is desirable. It is also likely that decreased frequency of dosing will decrease the burden of treatment and travel-related costs for patients, as well as for family and caregivers. It is expected that the monitoring required for BCG-unresponsive NMIBC will be the same for nadofaragene firadenovec as for other instillation therapies. Compared with pembrolizumab, a systemic therapy, nadofaragene firadenovec is likely to have less serious side effects and is given by urologists who have the infrastructure to provide instillation therapy.

Oportuzumab Monatox

The mechanism of action of oportuzumab monatox is new for the treatment of patients with BCG-unresponsive NMIBC. Given the single-arm study that evaluated it, how it compares to nadofaragene firadenovec, pembrolizumab, and gemcitabine with or without docetaxel is uncertain. The CR rates seen suggest that it will help some patients with this disease, but that most patients will end up with disease recurrence or progression over time. Administration of oportuzumab monatox is by instillation into the bladder, similar to other medications given for NMIBC.

The dosing schedule of oportuzumab monatox is more frequent than that of nadofaragene firadenovec and gemcitabine with or without docetaxel. As such, the burden of treatment and travel-related costs for patients, as well as family and caregivers, will be greater than for nadofaragene firadenovec and gemcitabine with or without docetaxel. It is expected that the monitoring required for BCG-unresponsive NMIBC will be the same for oportuzumab monatox as for other instillation therapies. Compared with pembrolizumab, a systemic therapy, oportuzumab monatox is likely to have less serious side effects and is given by urologists who have the infrastructure to provide instillation therapy.

QALY Shortfalls

One important contextual consideration to consider is the argument that society should give preference to treatments for patients with more severe conditions,[108] and that giving priority to

treatments according to "lifetime burden of illness" or "need" best represents the ethical instincts of a society or other decision-makers.[109,110] To inform this contextual consideration, ICER provides empirical results for the absolute QALY shortfall and proportional QALY shortfall. The absolute QALY shortfall is defined as the total absolute amount of future health patients with a condition are expected to lose without the treatment that is being assessed.[111] The ethical consequences of using absolute QALY shortfall to prioritize treatments is that conditions that cause early death or that have very serious lifelong effects on quality of life receive the greatest prioritization. Thus, certain kinds of treatments, such as treatments for rapidly fatal conditions of children, or for lifelong disabling conditions, score highest on the scale of absolute QALY shortfall.

The proportional QALY shortfall is measured by calculating the proportion of the total QALYs of remaining life expectancy that would be lost due to untreated illness.[112,113] The proportional QALY shortfall reflects the ethical instinct to prioritize treatments for patients whose illness would rob them of a large percentage of their expected remaining lifetime. As with absolute QALY shortfall, rapidly fatal conditions of childhood have high proportional QALY shortfalls, but the highest numbers can also often arise from severe conditions among the elderly who may have only a few years left of average life expectancy but would lose much of that to the illness without treatment.

For this population of adults with BCG-unresponsive, high risk NMIBC, the absolute shortfall was estimated to be 5.7 QALYs, with a proportional shortfall of 0.54, representing a loss of 54% of total quality-adjusted life expectancy (QALE) without the condition. To provide some anchoring of these results, we also present a league table of absolute and proportional QALY shortfalls for a variety of conditions from prior ICER reports (Table 6.2), using a burden of disease calculator developed by Dutch investigators (https://imta.shinyapps.io/iDBC/) that allows for calculation of absolute and proportional QALY shortfalls under different assumptions.[110]

Table 6.2. League Table of Absolute and Proportional QALY Shortfalls for Selected Conditions

	From ICER Reports			From iDBC tool[114]	
Condition	Age	% Male	Total Undiscounted QALYs with Standard of Care	Absolute Shortfall	Proportional Shortfall
BCG-Unresponsive High-Risk NMIBC	72	80	4.94	5.7	0.54
Secondary Progressive Multiple Sclerosis	48	39	3.0	24.5	0.89
Treatment-Resistant Major Depression	46	33	20.5	8.7	0.30
Cystic Fibrosis	2	52	25.8	42.3	0.62

QALY: quality-adjusted life year

7. Health Benefit Price Benchmarks

As described in section 5, there were discrepancies in the clinical trials of nadofaragene firadenovec and oportuzumab monatox in how recurrence was assessed at 12 months. For nadofaragene firadenovec, a biopsy was conducted in all patients, whereas for oportuzumab monatox, biopsies were not conducted. We therefore calculated two different scenarios: 1) an optimistic scenario excluding the recurrences identified by biopsy alone at the 12-month CR and HGRFS outcomes in both nadofaragene firadenovec and oportuzumab monatox studies; and 2) a pessimistic scenario assuming the recurrences identified by biopsy alone at the 12-month CR and HGRFS outcomes did happen in both the nadofaragene firadenovec and oportuzumab monatox studies. Therefore, in calculating the health-benefit price benchmarks, we included both scenarios for each threshold evaluated. Annual prices for nadofaragene firadenovec and oportuzumab monatox that would achieve incremental cost-effectiveness ratios of $100,000 and $150,000 per QALY or evLYG are presented in Tables 7.1 and 7.2, with corresponding prices per day shown in Appendix Tables E7 and E8. No wholesale acquisition costs are currently available for either product. Therefore, no estimates of required price discounts are provided.

Table 7.1. Annual Cost-Effectiveness Threshold Prices for Nadofaragene Firadenovec and Oportuzumab Monatox in Patients with CIS ± Ta/T1

Annual Prices Using…	Annual WAC	Annual Price at $100,000 Threshold	Annual Price at $150,000 Threshold
Nadofaragene Firadenovec			
QALYs Gained	N/A	$114,000-$120,100	$163,500-$172,300
evLYG	N/A	$125,300-$131,900	$180,500-$189,900
Oportuzumab Monatox			
QALYs Gained	N/A	$ 35,800-$41,000	$52,900-$60,400
evLYG	N/A	$39,700-$45,400	$58,700-$66,900

QALY: quality-adjusted life year; evLYG: equal value of life years gained; WAC: wholesale acquisition cost; N/A: not available

Table 7.2. Annual Cost-Effectiveness Threshold Prices for Nadofaragene Firadenovec and Oportuzumab Monatox in Patients with High Grade Ta/T1

Annual Prices Using…	Annual WAC	Annual Price at $100,000 Threshold	Annual Price at $150,000 Threshold
Nadofaragene Firadenovec			
QALYs Gained	N/A	$175,000-$185,700	$250,700-$265,900
evLYG	N/A	$ 189,700-$200,900	$272,600-$288,700
Oportuzumab Monatox			
QALYs Gained	N/A	$113,800-$124,900	$164,600-$180,500
evLYG	N/A	$124,200-$136,100	$180,200-$197,300

QALY: quality-adjusted life year; evLYG: equal value of life years gained; WAC: wholesale acquisition cost; N/A: not available

We have estimated that the eligible population for these treatments would be 73% Ta/T1 patients and 27% CIS patients (see section 8 below for details). Applying these proportions, we calculated the weighted average threshold prices across both populations (Table 7.3).

Table 7.3. Weighted Average Annual Cost-Effectiveness Threshold Prices for Nadofaragene Firadenovec and Oportuzumab Monatox across Patients with CIS ± Ta/T1 and High Grade Ta/T1

Annual Prices Using…	Annual WAC	Annual Price at $100,000 Threshold	Annual Price at $150,000 Threshold
Nadofaragene Firadenovec			
QALYs Gained	N/A	$158,600-$168,000	$227,200-$240,600
evLYG	N/A	$172,300-$182,300	$247,700-$262,000
Oportuzumab Monatox			
QALYs Gained	N/A	$92,800-$102,300	$134,500-$148,100
evLYG	N/A	$101,400-$111,600	$147,400-$162,100

QALY: quality-adjusted life year; evLYG: equal value of life years gained; WAC: wholesale acquisition cost; N/A: not available

The ICER health benefit price benchmark (HBPB) is a price range suggesting the highest price a manufacturer should charge for a treatment, based on the amount of improvement in overall health patients receive from that treatment, when a higher price would cause disproportionately greater losses in health among other patients due to rising overall costs of health care and health insurance. In short, it is the top price range at which a health system can reward innovation and better health for patients without doing more harm than good.

The HBPB range for nadofaragene firadenovec across both scenarios and both populations would range from $158,600 to $262,000 per year. The HBPB range for oportuzumab monatox ranges from $92,800 to $162,100 per year. Note that determining an appropriate and fair health-benefit based price for this heterogeneous group of patients is made even more difficult by not having evidence on potential comparators, and that our base case assumption of no benefit to comparator therapy means the estimates above should be considered as upper bounds on prices.

8. Potential Budget Impact

8.1 Overview

We used results from the cost-effectiveness model to estimate the potential total budgetary impact of treatment with nadofaragene firadenovec or oportuzumab monatox for adults 18 years and older with BCG-unresponsive/refractory, high risk NMIBC, graded as CIS ± Ta/T1 or non-CIS with HG Ta/T1. As these products are under FDA review and prices have not been announced by the manufacturers, we used assumed placeholder prices and the three population-weighted threshold prices (at $50,000, $100,000, and $150,000 per QALY) for nadofaragene firadenovec and oportuzumab monatox in our estimates of budget impact. Pembrolizumab was not included in this analysis because of its established presence in the market.

The aim of the potential budgetary impact analysis is to document the percentage of patients who could be treated at selected prices without crossing a potential budget impact threshold that is aligned with overall growth in the US economy. For 2019-2020, the five-year annualized potential budget impact threshold that should trigger policy actions to manage access and affordability is calculated to be approximately $819 million per year for new drugs.

8.2 Methods

We used results from the same model employed for the cost-effectiveness analyses to estimate total potential budget impact. Potential budget impact was defined as the total differential cost of using each new therapy rather than relevant existing therapy for the treated population, calculated as differential health care costs (including drug costs) minus any offsets in these costs from averted health care events. All costs were undiscounted and estimated over a five-year time horizon, given the potential for cost offsets to accrue over time and to allow a more realistic impact on the number of patients treated with the new therapy.

The potential budget impact analysis includes the estimated number of individuals in the US who would be eligible for these treatments. To estimate the size of the potential candidate population for treatment, we used the total number of adults 18 years and older with BCG-unresponsive/refractory, high risk NMIBC, graded as CIS ± Ta/T1 or non-CIS with HG Ta/T1.

Overall, bladder cancer is the sixth most common cancer in the US, with approximately 80,000 new cases each year and 17,700 deaths.[1,2] The National Cancer Institute's Surveillance, Epidemiology and End Results Program (SEER) estimates that prevalence of bladder cancer was 712,614 people in the US in 2017.[2] Kirkali et al. estimated that approximately 70% of bladder cancers present as NMIBC, with approximately 70% classified as Ta, 20% as T1, and 10% as CIS.[7] We assumed that T1 and CIS are considered high-grade disease while 10% of Ta cancers are considered high grade.[32] For

the proportion of patients who are BCG-unresponsive/refractory, we assumed that approximately 38% will be classified as BCG non-responders.[33] Applying these proportions to the estimated prevalent NMIBC population (712,614), we arrived at an estimate of 70,135 individuals as the eligible population for these treatments, with 73% (51,180) being Ta and T1 patients and 27% (18,956) being CIS patients. Among these eligible patients, we assumed a 20% uptake each year over five years, or 14,027 patients per year.

We evaluated whether the new treatments would take market share from one or more existing treatments to calculate the blended budget impact associated with displacing use of existing therapies with the new intervention. In this analysis, we assumed that patients eligible for nadofaragene firadenovec or oportuzumab monatox would otherwise have been treated with "usual care" as typified by the hypothetical treatment used in the base case (i.e., no specific bladder cancer-related treatment).

ICER's methods for estimating potential budget impact are described in detail elsewhere[115] and have been recently updated. The intent of our revised approach to potential budgetary impact is to document the percentage of patients who could be treated at selected prices without crossing a potential budget impact threshold that is aligned with overall growth in the US economy. For 2019-2020, the five-year annualized potential budget impact threshold that should trigger policy actions to manage access and affordability is calculated to be approximately $819 million per year for new drugs.

8.3 Results

Figure 8.1 illustrates the cumulative per-patient budget impact calculations for nadofaragene firadenovec and oportuzumab monatox compared to the "usual care" comparator, based on the assumed placeholder prices of $164,337 and $150,000 per one year of treatment, respectively. The average potential budgetary impact for nadofaragene firadenovec was an additional per-patient cost of approximately $128,000 in year one, with net annual savings in following years leading to cumulative costs per patient of approximately $98,000 by year five. The average potential budgetary impact for oportuzumab monatox followed a similar pattern, with an additional per-patient cost of approximately $123,000 in year one and net savings in following years leading to cumulative costs per patient of approximately $101,000 by year five. Additional net costs per year are presented along with cumulative net costs in Appendix Table E6.

Figure 8.1. Cumulative Net Cost Per Patient Treated with Nadofaragene Firadenovec and Oportuzumab Monatox at Assumed Placeholder Price Over a Five-Year Time Horizon

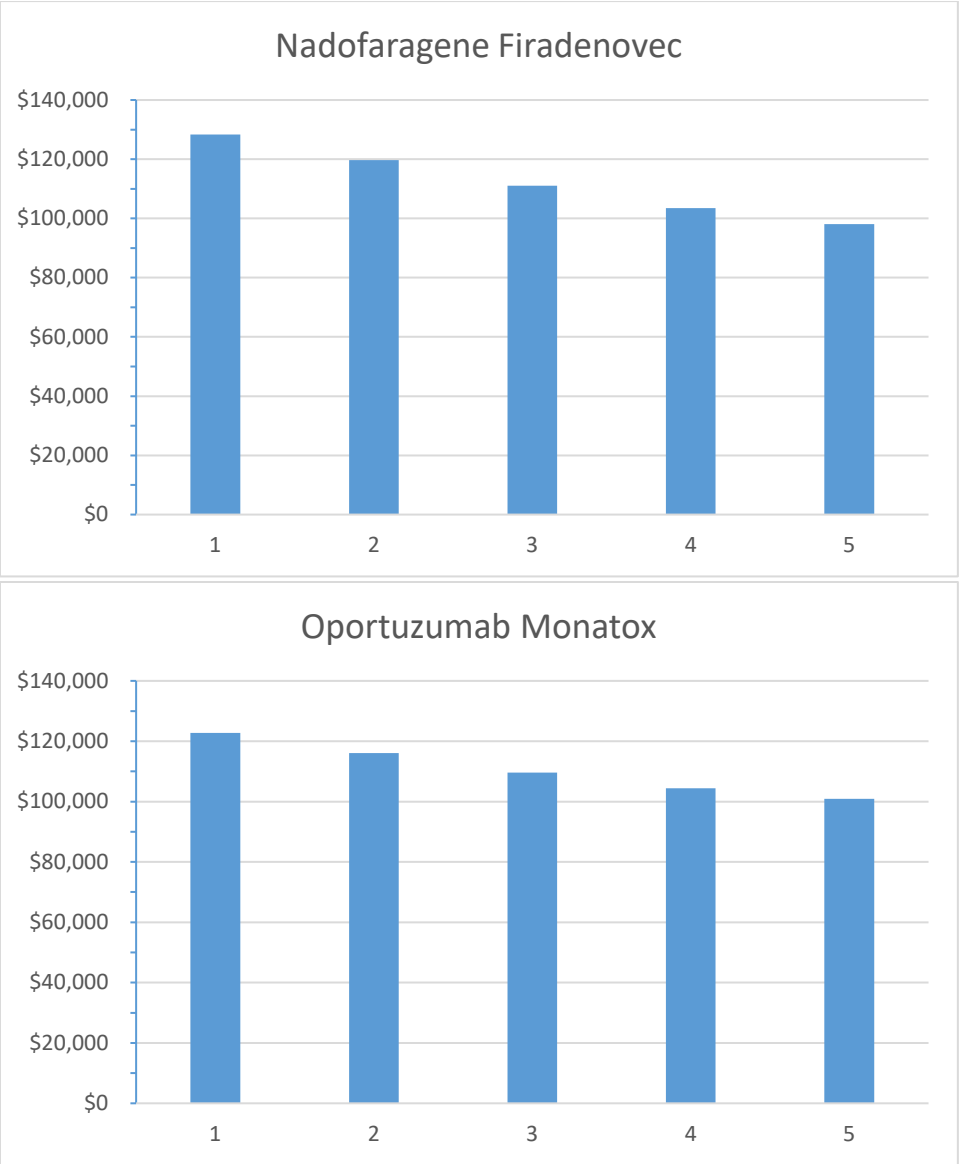


Figure 8.2 illustrates the potential budget impact of nadofaragene firadenovec treatment of the eligible population, based on the assumed placeholder price ($164,337 per year of treatment), and the weighted-average prices to reach $150,000, $100,000, and $50,000 per QALY (approximately $227,100, $158,500, and $90,000 per year of treatment, respectively) compared to the "usual care" comparator. As shown in Figure 8.2, approximately 52% of eligible patients could be treated in a given year without crossing the ICER budget impact threshold of $819 million at the assumed placeholder price. Approximately 36% of patients could be treated in a given year without crossing the budget impact threshold at the $150,000 per QALY threshold price, while approximately 54% of the population could be treated without crossing the threshold at the $100,000 per QALY threshold

price. All eligible patients could be treated at the $50,000 per QALY threshold price, with potential budget impact reaching 90% of the potential budget impact threshold.

Figure 8.2. Budgetary Impact of Nadofaragene Firadenovec in BCG-Unresponsive/Refractory, High Risk NMIBC Patients

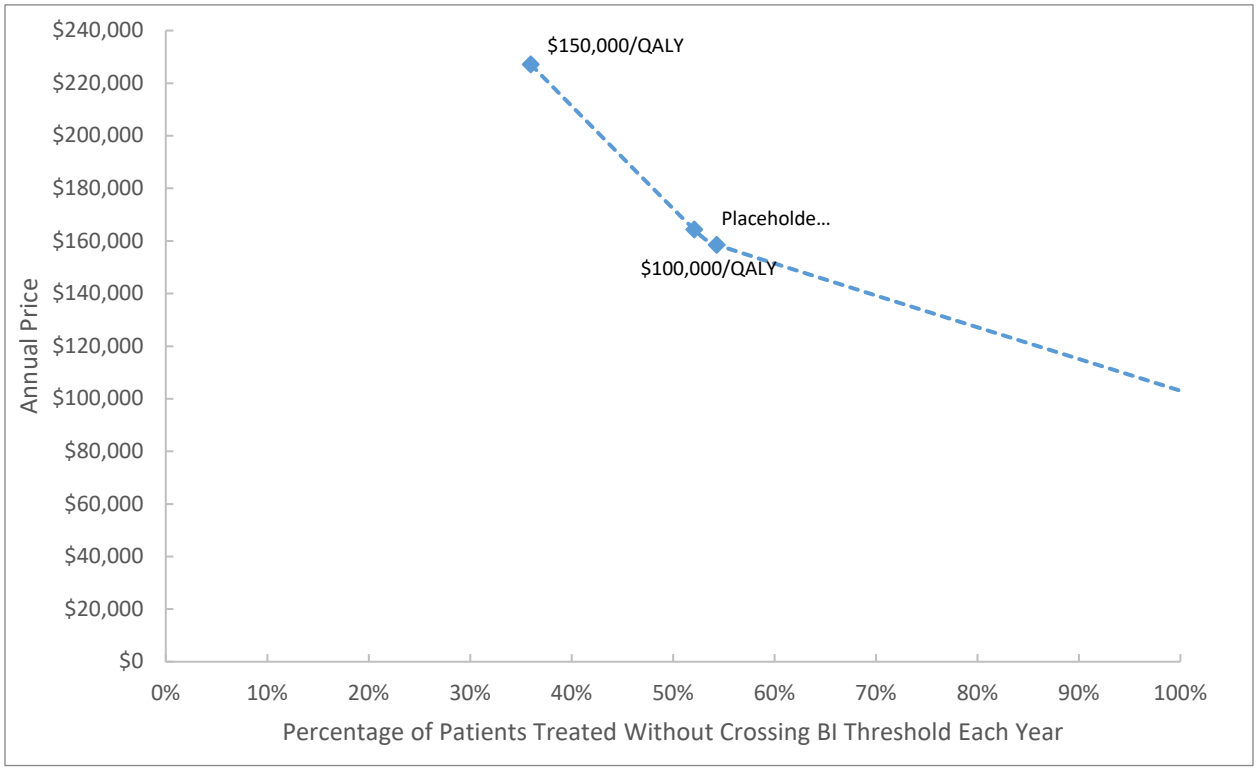
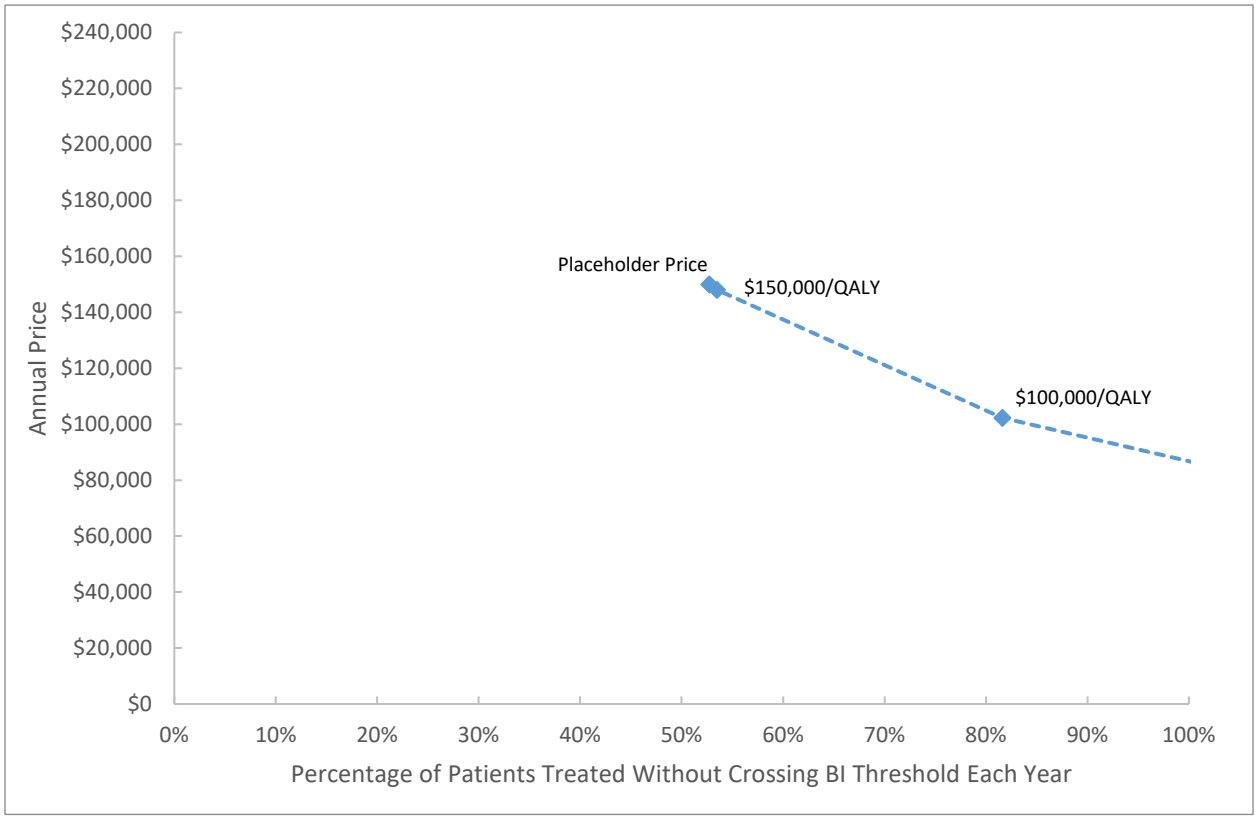


Figure 8.3 illustrates the potential budget impact of oportuzumab monatox treatment of the eligible population, based on the assumed net price ($150,000 per year), and the weighted-average prices to reach $150,000, $100,000, and $50,000 per QALY (approximately $148,0000, $102,200, and $56,400 per year of treatment, respectively) compared to usual care. As shown in Figure 8.3, approximately 53% of eligible patients could be treated in a given year without crossing the ICER budget impact threshold of $819 million at the assumed placeholder price. Approximately 54% of patients could be treated in a given year without crossing the budget impact threshold at the $150,000 per QALY threshold price, while approximately 82% of the population could be treated without crossing the threshold at the $100,000 per QALY threshold price. All eligible patients could be treated at the $50,000 per QALY threshold price, with potential budget impact reaching 58% of the threshold.

Figure 8.3. Budgetary Impact of Oportuzumab Monatox in BCG-Unresponsive/Refractory, High Risk NMIBC Patients



9. Summary of the Votes and Considerations for Policy

9.1 About the Midwest CEPAC Process

During Midwest CEPAC public meetings, the CEPAC Panel deliberates and votes on key questions related to the systematic review of the clinical evidence, an economic analysis of the applications of treatments under examination, and the supplementary information presented. Panel members are not pre-selected based on the topic being addressed and are intentionally selected to represent a range of expertise and diverse perspectives.

Acknowledging that any judgment of evidence is strengthened by real-life clinical and patient perspectives, subject matter experts are recruited for each meeting topic and provide input to the Midwest CEPAC Panel members before the meeting to help clarify their understanding of the different interventions being analyzed in the evidence review. The same clinical experts serve as a resource to the Midwest CEPAC Panel during their deliberation and help to shape recommendations on ways the evidence can apply to policy and practice.

After the Midwest CEPAC Panel votes, a policy roundtable discussion is held with the Midwest CEPAC Panel, clinical experts, patient advocates, payers, and when feasible, manufacturers. The goal of this discussion is to bring stakeholders together to apply the evidence to guide patient education, clinical practice, and coverage and public policies. Participants on policy roundtables are selected for their expertise on the specific meeting topic, are different for each meeting, and do not vote on any questions.

At the November 20 meeting, the Midwest CEPAC Panel discussed issues regarding the application of the available evidence to help patients, clinicians, and payers address important questions related to the use of Nadofaragene Firadenovec and Oportuzumab Monatox for BCG-Unresponsive, Non-Muscle Invasive Bladder Cancer. Following the evidence presentation and public comments (public comments from the meeting can be accessed here, the Midwest CEPAC Panel voted on key questions concerning the comparative clinical effectiveness, comparative value, and potential other benefits and contextual considerations related to Nadofaragene Firadenovec and Oportuzumab Monatox. These questions are developed by the ICER research team for each assessment to ensure that the questions are framed to address the issues that are most important in applying the evidence to support clinical practice, medical policy decisions, and patient decision-making. The voting results are presented below, along with specific considerations mentioned by the Midwest CEPAC Panel members during the voting process. Of note, some results in this Report, particularly in the sections looking at economic analyses and at adverse events, were updated or corrected

after the public meeting. We believe it is unlikely that these changes would have substantially affected the voting that occurred, but readers of this Report should be aware of this timing.

In its deliberations and votes related to value, the Midwest CEPAC Panel considered the individual patient benefits, and incremental costs to achieve such benefits, from a given intervention over the long term.

There are four elements to consider when deliberating on long-term value for money (see Figure 9.1 below):

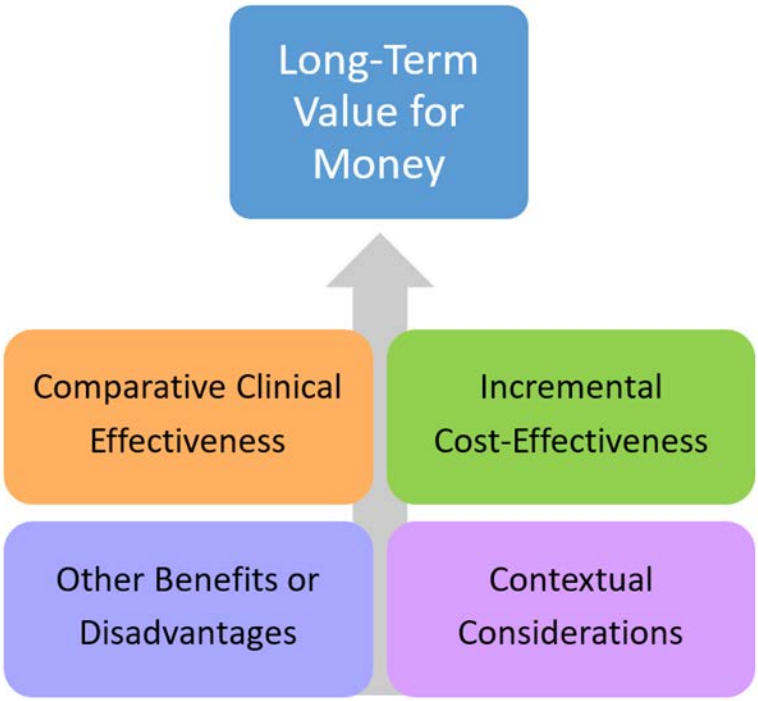
- Comparative clinical effectiveness is a judgment of the overall difference in clinical outcomes between two interventions (or between an intervention and placebo), tempered by the level of certainty possible given the strengths and weaknesses of the body of evidence. The Midwest CEPAC uses the ICER Evidence Rating Matrix as its conceptual framework for considering comparative clinical effectiveness.

- Estimated incremental cost-effectiveness is the average incremental cost per patient of one intervention compared to another to achieve a desired "health gain," such as an additional stroke prevented, case of cancer diagnosed, or gain of a year of life. Alternative interventions are compared in terms of cost per unit of effectiveness, and the resulting comparison is presented as a cost-effectiveness ratio. Relative certainty in the cost and outcome estimates continues to be a consideration. As a measure of cost-effectiveness, the Midwest CEPAC voting panel follows common academic and health technology assessment standards by using cost per quality-adjusted life year (QALY), with formal voting on "long-term value for money" when the base case incremental cost-effectiveness ratio is between $50,000 per QALY and $175,000 per QALY.

- Potential other benefits refer to any significant benefits or disadvantages offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that would not have been considered as part of the evidence on comparative clinical effectiveness. Examples of potential other benefits include better access to treatment centers, mechanisms of treatment delivery that require fewer visits to the clinician's office, treatments that reduce disparities across various patient groups, and new potential mechanisms of action for treating clinical conditions that have demonstrated low rates of response to currently available therapies. Other disadvantages could include increased burden of treatment on patients or their caregivers. For each intervention evaluated, it will be open to discussion whether potential other benefits or disadvantages such as these are important enough to factor into the overall judgment of long-term value for money. There is no quantitative measure for potential other benefits or disadvantages.

- Contextual considerations include ethical, legal, or other issues (but not cost) that influence the relative priority of illnesses and interventions. Examples of contextual considerations include whether there are currently any existing treatments for the condition, whether the condition severely affects quality of life or not, and whether there is significant uncertainty about the magnitude of benefit or risk of an intervention over the long term. There is no quantitative measure for contextual considerations.

Figure 9.1. Conceptual Structure of Long-Term Value for Money



9.2 Voting Results

Patient population for questions 1-5: Adults with BCG-unresponsive, high-risk NMIBC (CIS ±Ta/T1 or non-CIS with high grade Ta/T1)

1. **Is the evidence adequate to demonstrate that the net health benefit of nadofaragene firadenovec is superior to that provided by best supportive care?**

Yes: 7 votes	No: 4 votes

The majority of the Council judged that the evidence was adequate to demonstrate that the net health benefit of nadofaragene firadenovec is superior to that provided by best supportive care, primarily because the Phase III trial showed reductions in recurrence and progression over time that exceeded the FDA threshold for effectiveness. Council members who voted "No" may have done so because of the lack of long-term data and potential for losing the window of curability through cystectomy should nadofaragene firadenovec not prevent recurrence.

2. **Is the evidence adequate to demonstrate that the net health benefit of oportuzumab monatox is superior to that provided by best supportive care?**

Yes: 8 votes	No: 3 votes

The majority of the Council judged that the evidence was adequate to demonstrate that the net health benefit of oportuzumab monatox is superior to that of best supportive care, for similar reasons as were discussed for nadofaragene firadenovec.

3. **Is the evidence adequate to distinguish the net health benefit of nadofaragene firadenovec from oportuzumab monatox?**

Yes: 0 votes	***No: 11 votes***

The Council unanimously judged that the evidence was inadequate to demonstrate the net health benefit of nadofaragene firadenovec from oportuzumab monatox. The Council's vote was based on the lack of comparative data between nadofaragene firadenovec and oportuzumab monatox.

4. **Is the evidence adequate to demonstrate that the net health benefit of nadofaragene firadenovec is superior to that provided by gemcitabine with or without docetaxel?**

Yes: 0 votes	***No: 11 votes***

The Council unanimously judged that the evidence was inadequate to demonstrate that the net health benefit of nadofaragene firadenovec is superior to that provided by gemcitabine with or without docetaxel. Differences in the populations and outcomes assessed in the retrospective trials of gemcitabine with docetaxel precluded comparison with nadofaragene firadenovec.

Please note that this voting result does not match the meeting recording, because one Council member had entered their vote incorrectly through the voting software.

5. **Is the evidence adequate to demonstrate that the net health benefit of oportuzumab monatox is superior to that provided by gemcitabine with or without docetaxel?**

Yes: 0 votes	***No: 11 votes***

The Council unanimously voted that the evidence is not adequate to demonstrate that the net health benefit of oportuzumab monatox is superior to that provided by gemcitabine with or without docetaxel, for the reasons discussed above.

Patient population for questions 6-7: Adults with BCG-unresponsive, high-risk NMIBC with CIS ± Ta/T1

6. **Is the evidence adequate to demonstrate that the net health benefit of nadofaragene firadenovec is superior to that provided by systemic pembrolizumab?**

Yes: 0 votes	***No: 11 votes***

The Council unanimously judged that the evidence was inadequate to demonstrate that the net health benefit of nadofaragene firadenovec is superior to that provided by systematic pembrolizumab because the single-arm trials did not have a placebo group or active comparator, and had slight differences in study populations and how outcomes were assessed. In addition, the trial for nadofaragene firadenovec required a biopsy at 12 months, while the pembrolizumab trial did not.

7. Is the evidence adequate to demonstrate that the net health benefit of oportuzumab monatox is superior to that provided by systemic pembrolizumab?

Yes: 1 vote	***No: 10 votes***

The majority of the Council voted that the evidence was not adequate to demonstrate that the net health benefit of oportuzumab monatox is superior to that provided by systemic pembrolizumab, for similar issues as described above. However, at 12 months, the outcome assessments for oportuzumab and pembrolizumab were done similarly with cystoscopy and cytology, and neither required a biopsy. The CR rates at 12 months were identical for the two drugs.

For questions 8, 9 and 10: Please vote 1, 2, or 3 on the following potential other benefits and contextual considerations as they relate to nadofaragene firadenovec and oportuzumab monatox.

Question 8

1 (Suggests Lower Value)	2 (Intermediate)	3 (Suggests Higher Value)
This intervention will not differentially benefit a historically disadvantaged or underserved community		This intervention will differentially benefit a historically disadvantaged or underserved community
5 votes	***6 votes***	0 votes

All Council members voted either that the interventions will not differentially benefit a historically disadvantaged community, or that there will be an intermediate benefit.

Question 9

1 (Suggests Lower Value)	2 (Intermediate)	3 (Suggests Higher Value)
Small health loss without this treatment as measured by absolute QALY shortfall.		Substantial health loss without this treatment as measured by absolute QALY shortfall.
4 votes	***4 votes***	3 votes

The Council votes were split between a small, intermediate, and substantial health loss as measured by absolute QALY shortfall. The Council discussed how this condition primarily affects older individuals, who have a relatively quality-adjusted life expectancy.

Question 10

1 (Suggests Lower Value)	2 (Intermediate)	3 (Suggests Higher Value)
Small health loss without this treatment as measured by proportional QALY shortfall.		Substantial health loss without this treatment as measured by proportional QALY shortfall.
1 vote	***7 votes***	3 votes

The majority of Council members voted that there would be an intermediate health loss without treatment for patients in this population, as measured by proportional QALY shortfall. The Council voted based on the proportional quality-adjusted life expectancy that would be lost without any additional treatment, which is 54%.

11. Please vote 1, 2, or 3 on the following potential other benefits and contextual considerations as they relate to nadofaragene firadenovec.

1 (Suggests Lower Value)	2 (Intermediate)	3 (Suggests Higher Value)
Uncertainty or overly favorable model assumptions creates significant risk that base-case cost-effectiveness estimates are too optimistic		Uncertainty or overly unfavorable model assumptions creates significant risk that base-case cost-effectiveness estimates are too pessimistic
2 votes	***7 votes***	2 votes

The majority of the Council voted that the model assumptions for nadofaragene firadenovec were neither overly favorable nor unfavorable. The Council based their votes on the high levels of uncertainty in the model, due to the lack of available data and how the model favors highly unstable longer-term outcomes. There is also uncertainty in the assumption that the hypothetical comparator has a 0% response rate.

12. Please vote 1, 2, or 3 on the following potential other benefits and contextual considerations as they relate to oportuzumab monatox.

1 (Suggests Lower Value)	2 (Intermediate)	3 (Suggests Higher Value)
Uncertainty or overly favorable model assumptions creates significant risk that base-case cost-effectiveness estimates are too optimistic		Uncertainty or overly unfavorable model assumptions creates significant risk that base-case cost-effectiveness estimates are too pessimistic
2 votes	***7 votes***	1 vote

The majority of the Council voted that the base-case model assumptions were neither overly favorable nor unfavorable for oportuzumab monatox, for the same reasons as discussed in the previous question. Please note that one Council member was not available to vote on this question.

13. Please vote 1, 2, or 3 on the following potential other benefits and contextual considerations as they relate to nadofaragene firadenovec.

1 (Suggests Lower Value)	2 (Intermediate)	3 (Suggests Higher Value)
Very similar mechanism of action to that of other active treatments		New mechanism of action compared to that of other active treatments
0 votes	3 votes	***7 votes***

The majority of the Council voted that nadofaragene firadenovec represents a new mechanism of action, because of its novel delivery mechanism compared to existing treatments. Please note that one Council member was not available to vote on this question.

14. Please vote 1, 2, or 3 on the following potential other benefits and contextual considerations as they relate to oportuzumab monatox.

1 (Suggests Lower Value)	2 (Intermediate)	3 (Suggests Higher Value)
Very similar mechanism of action to that of other active treatments		New mechanism of action compared to that of other active treatments
0 votes	3 votes	***7 votes***

The majority of the Council voted that oportuzumab monatox represents a new mechanism of action, again because of its novel mechanism of delivery into the cell compared to existing treatments and to nadofaragene firadenovec. Please note that one Council member was not available to vote on this question.

15. Please vote 1, 2, or 3 on the following potential other benefits and contextual considerations as they relate to nadofaragene firadenovec.

1 (Suggests Lower Value)	2 (Intermediate)	3 (Suggests Higher Value)
Delivery mechanism or relative complexity of regimen likely to lead to much lower real-world adherence and worse outcomes relative to an active comparator than estimated from clinical trials		Delivery mechanism or relative simplicity of regimen likely to result in much higher real-world adherence and better outcomes relative to an active comparator than estimated from clinical trials
0 votes	3 votes	***7 votes***

The majority of the Council voted that the relative simplicity of the treatment regimen for nadofaragene firadenovec is likely to result in much higher real-world adherence and better outcomes relative to other treatment options. Earlier in the discussion, one patient expert emphasized that the infrequent instillation schedule for nadofaragene firadenovec could provide a benefit for patients, who previously had to receive frequent instillations of BCG or other agents. One clinical expert also noted that the intensity of instillation schedules for existing treatments has a negative impact on adherence, particularly in rural communities. Please note that one Council member was not available to vote on this question.

16. Please vote 1, 2, or 3 on the following potential other benefits and contextual considerations as they relate to oportuzumab monatox

1 (Suggests Lower Value)	2 (Intermediate)	3 (Suggests Higher Value)
Delivery mechanism or relative complexity of regimen likely to lead to much lower real-world adherence and worse outcomes relative to an active comparator than estimated from clinical trials		Delivery mechanism or relative simplicity of regimen likely to result in much higher real-world adherence and better outcomes relative to an active comparator than estimated from clinical trials
0 votes	***8 votes***	2 votes

The majority of Council members judged that the treatment regimen for oportuzumab monatox would likely lead neither to higher nor lower real-world adherence than for existing therapies. It was noted that the treatment regimen for oportuzumab monatox is more or less comparable to existing therapies and chemotherapeutics. Please note that one Council member was not available to vote on this question.

17. Please vote 1, 2, or 3 on the following potential other benefits and contextual considerations as they relate to nadofaragene firadenovec

1 (Suggests Lower Value)	2 (Intermediate)	3 (Suggests Higher Value)
Will not significantly reduce the negative impact of the condition on family and caregivers vs. the comparator		Will significantly reduce the negative impact of the condition on family and caregivers vs. the comparator
1 vote	***9 votes***	0 votes

The majority of the Council voted that nadofaragene firadenovec will moderately reduce the negative impact of the condition on family and caregivers. The Council discussed that the less frequent treatment regimen and potential effectiveness in preventing recurrence could benefit families and caregivers, who may be responsible for bringing patients to their appointments. Please note that one Council member was not available to vote on this question.

18. Please vote 1, 2, or 3 on the following potential other benefits and contextual considerations as they relate to oportuzumab monatox

1 (Suggests Lower Value)	2 (Intermediate)	3 (Suggests Higher Value)
Will not significantly reduce the negative impact of the condition on family and caregivers vs. the comparator		Will significantly reduce the negative impact of the condition on family and caregivers vs. the comparator
2 votes	***8 votes***	0 votes

The majority of the Council voted that oportuzumab monatox will moderately reduce the negative impact of the condition on family and caregivers, for similar issues as were discussed above. Please note that one Council member was not available to vote on this question.

19. Please vote 1, 2, or 3 on the following potential other benefits and contextual considerations as they relate to nadofaragene firadenovec and oportuzumab monatox

1 (Suggests Lower Value)	2 (Intermediate)	3 (Suggests Higher Value)
Will not have a significant impact on improving return to work and/or overall productivity vs. the comparator		Will have a significant impact on improving return to work and/or overall productivity vs. the comparator
3 votes	***7 votes***	1 vote

The majority of Council members voted that both treatments will have a moderate impact on the ability of patients to return to work. One clinical expert and council member discussed how if the treatments are effective, patients will be able to reduce their number of visits to the clinic for treatment and surveillance. In addition, one

patient expert discussed how the potential complications from a cystectomy can affect the daily lives of patients, so preventing cystectomy could provide a large benefit to productivity.

9.3 Roundtable Discussion and Key Policy Implications

Following its deliberation on the evidence, the Midwest CEPAC Panel engaged in a moderated discussion with a policy roundtable about how best to apply the evidence on Nadofaragene Firadenovec and Oportuzumab Monatox for BCG-Unresponsive, Non-Muscle Invasive Bladder Cancer to policy and practice. The policy roundtable members included 2 patients, 2 clinical experts, 2 payers, and 2 representatives from pharmaceutical manufacturers. The discussion reflected multiple perspectives and opinions, and therefore, none of the statements below should be taken as a consensus view held by all participants. The names of the Policy Roundtable participants are shown below, and conflict of interest disclosures for all meeting participants can be found in Appendix G.

Table 9.1. Policy Roundtable Members

Names	Title and Affiliation
Stephanie Chisolm, PhD	Director of Education and Research, Bladder Cancer Advocacy Network
Rachelle Dillon, PhD	Director, Clinical Operations, Sesen Bio
Leslie Fish, RPh, PharmD	Vice President of Clinical Pharmacy, IPD Analytics
John Gore, MD, MS, FACS	Associate Professor, Department of Urology; Adjunct Associate Professor, Department of Surgery, University of Washington
John W. McKnight, PharmD, BCPS	Vice President, HPS Clinical and Specialty Strategies, Humana
Aaron Mitchell, MD, MPH	Assistant Attending, Medical Oncologist, Memorial Sloan Kettering Cancer Center
Karen Sachse, RN, MSN	Patient Advocate
Kristen Wachsmuth, DHSc, MBA	Senior Director, Medical Affairs & Clinical Development, FerGene

The roundtable discussion was facilitated by Dr. Steven Pearson, MD, MSc, President of ICER. The main themes and recommendations from the discussion are organized by audience and summarized below.

Introduction

The following policy recommendations reflect the main themes and points made during the Policy Roundtable discussion at the November 20, 2020 Midwest CEPAC public meeting on the use of nadofaragene firadenovec and oportuzumab monatox for the treatment of BCG-unresponsive non-muscle invasive bladder cancer (NMIBC). At the meeting, ICER presented the findings of its revised report on these treatments and the Midwest CEPAC voting council deliberated on key questions related to their comparative clinical effectiveness, potential other benefits, and contextual considerations. Following the votes, ICER convened a Policy Roundtable of two patient advocates,

two clinical experts, two payers, and two pharmaceutical manufacturer representatives to discuss how best to apply the evidence and votes to real-world practice and policy. The discussion reflected multiple perspectives and opinions, and therefore, none of the statements below should be taken as a consensus view held by all participants.

A recording of the conversation can be accessed here, https://youtu.be/L3zlkjirq_o, and recordings of the voting portion of the meeting can be accessed here, https://youtu.be/UUwe7sY87Uw, and here, https://youtu.be/a5RUPqE-pqQ. More information on Policy Roundtable participants, including conflict of interest disclosures, can be found in the appendix of this document. ICER's final report on these treatments, which includes the same policy recommendations, can be found here, https://www.youtube.com/watch?v=L3zlkjirq_o.

The roundtable discussion was facilitated by Dr. Steven Pearson, MD, MSc, President of ICER. The main themes and recommendations from the discussion are organized by audience and summarized below.

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. Options for specific elements of coverage criteria within insurance coverage policy are discussed below.

Clinical Considerations

Patient Eligibility Criteria

a. **Patient population:** Given that trials of nadofaragene firadenovec and oportuzumab monatox included only patients with BCG-unresponsive NMIBC, it would be expected for the FDA labels for both treatments to be limited to these patients. BCG-unresponsive NMIBC broadly includes patients with refractory disease while receiving treatment or those with relapsing disease following at least two treatment courses. It is not clear whether the FDA labels will explicitly include "BCG-intolerant" patients, but clinicians are likely to view these patients as potentially eligible for treatment with the newer agents. Payers may therefore wish to consider requiring documentation of a trial of BCG as a criterion for coverage.
b. **Diagnosis:** Patients with BCG-unresponsive NMIBC were required to have had biopsy evidence of 1) carcinoma in situ (CIS) or 2) high grade papillary (Ta) or superficially invasive (T1) disease alone. Patients with CIS could also have Ta/T1 disease.

c. **Exclusion criteria:** Patients whose biopsy showed low/moderate grade Ta/T1 disease alone were excluded from the clinical trials. It is not yet known whether the FDA label will specify the pathological grade of NMIBC.

Step Therapy: As mentioned, it seems likely that the FDA label for the emerging treatments will be limited to patients who are unresponsive to BCG. Given that the evidence base is too limited to be able to distinguish the clinical effectiveness among nadofaragene firadenovec, oportuzumab monatox, pembrolizumab, and standard chemotherapy options (e.g., gemcitabine/docetaxel), the question will arise whether payers should consider "economic" step therapy to seek cost savings. This question is highly pertinent given the dramatic cost differences that are likely to exist between the inexpensive chemotherapy regimens and the newer treatment options.

We heard testimony from clinical experts that there would likely be wide variation in selection of treatment regimens across the country among the available treatments for BCG-unresponsive NMIBC. But there are important differences in the types of side effects, regimen complexity, and location of treatment that would lead patients to have strong preferences for certain treatment options. We heard that clinicians may view step therapy as more clinically acceptable for patients with high grade Ta/T1 disease alone since these patients demonstrate better outcomes with all treatments than patients with CIS disease. But there remains a strong culture of unrestricted treatment choice among the clinicians providing these treatments, making it likely that step therapy would be resisted. As a result, despite the lack of evidence demonstrating the superiority of any treatment modality, and the substantial cost savings that would accrue with first step use of chemotherapy, analysts believe only a minority of payers (10-20%) will ultimately implement step therapy for this population.

Manufacturers

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.

Patients highlighted the dramatic impact that BCG-unresponsive NMIBC can have on all aspects of life. Bladder cancer and its treatment and side effects can disrupt personal relationships with friends and family, and one's ability to function at home and work. Moreover, since most patients will progress or recur with nadofaragene firadenovec and oportuzumab monatox treatment over time, it is unclear if delaying potentially curative cystectomy risk loss of cure and more metastatic

disease and disease-related mortality. Comparative studies are needed to assess whether new treatments are effective in improving these important outcomes.

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.

To merit a similar or higher price, a new therapy requires better evidence on the comparative effectiveness and long-term benefit relative to existing treatments for the same condition. The potential for the new therapies to offer significant cost offsets, such as delaying or preventing cystectomy or metastatic disease, are promising, but require better evidence to merit higher prices. Substantial uncertainty should lower the threshold price and lead manufacturers to select a lower price while waiting for better data.

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.

Patients have the most to gain from better evidence on the comparative safety and effectiveness of new treatments. Bladder cancer advocacy groups should be applauded for their efforts to support research, raise awareness, and fight for improved access to effective treatments. Now that there is a healthy pipeline of new treatments emerging, patient groups should expand their focus to include advocacy for better research design so that patient-relevant outcomes are consistently measured across all studies, and so that the studies themselves are designed to support direct or robust indirect comparisons of the treatment options that patients will have.

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.

Patient groups should recognize that high prices contribute to financial toxicity for the patients they represent, for other patients with other illnesses, and for all of society.

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.

Choice of treatment for BCG-unresponsive NMIBC should be driven to a large degree by patient preference for delivery mechanism (intravenous versus intravesical), treatment schedule and burden, risks and benefits, and other factors through a shared decision-making process between the patient and provider. For treatments such as nadofaragene firadenovec and oportuzumab monatox that are administered by specialists as part of outpatient care, the high cost of buying these drugs can be a potential barrier to access for patients with BCG-unresponsive non-muscle invasive bladder cancer. Providers should be protected from the cost of buying these expensive drugs and at the same time, paying providers based upon a percentage of the drug's cost would create perverse incentives for their use. In such a situation, the provider gets more for administering more expensive therapies. Protecting providers from the cost of acquiring the therapy and then providing an adequate administration fee can ensure appropriate access for patients who may benefit from these therapies.

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.

The availability of new medications for BCG-unresponsive NMIBC with novel mechanisms of action point to a potentially major change in clinical practice. Placing these new agents into practice and helping clinicians identify their role in a rapidly changing landscape is critical. Since most patients with BCG-unresponsive NMIBC are treated with instillation therapies or surgery by urologists, multi-disciplinary collaboration with medical oncologists will be increasingly important as systemic therapies such as pembrolizumab become an option for similar patient populations.

Clinical experts also highlighted that limited evidence supporting existing therapies has led to lack of agreement about current standard therapy that is reflected in current guideline recommendations. It is important for professional societies to update clinical practice guidelines, especially in the setting of potentially major changes in available therapies. A key aspect of these efforts is to ensure that guidelines are developed using rigorous methods that include input from a range of experts, patients with the condition, as well as explicit disclosure and monitoring of

potential conflicts of interest. Guidelines should also highlight the role for shared decision making between providers and patients.

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.

Nadofaragene firadenovec and oportuzumab monatox demonstrate responses that appear greater than would be expected based upon historical data and there were few serious harms reported with low discontinuation rates. However, single arm studies that lack comparative data, differences among studies in terms of patients enrolled, outcome definitions and study methods, and limited long-term follow-up result in uncertainty about the magnitude of benefit of these new agents compared to best supportive care or other comparators. For all these reasons, clinical experts during the roundtable discussion highlighted the challenge of selecting which therapies to use in which patient. The FDA should no longer accept single-arm trials as the basis for regulatory approval of NMIBC therapies.

Researchers

Researchers should compare nadofaragene firadenovec and oportuzumab monatox to other therapies in randomized trials of patients with BCG-NMIBC.

Comments during the policy roundtable highlighted some of the important research gaps that limit identifying the best treatment for an individual patient. Though the decision to perform single-arm trials was permitted by the FDA, it limits the comparative assessment of outcomes and instead bases improvement on historical data that may not reflect current best supportive care. Data presented at the meeting on gemcitabine with or without docetaxel suggested that benefits and side effects that may be similar to nadofaragene firadenovec and oportuzumab monatox, but at a much lower cost. Assessing primary outcomes in controlled, active comparator studies would help address this issue.

Researchers 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.

The use of single-arm trials with primary outcomes assessed at 6 months for FDA approval does not lead to comparative data that relate to how these new medications will be used in clinical practice. Patient and experts highlighted the need for therapies that can effectively and safely delay or ideally prevent the need for cystectomy. For those with BCG-unresponsive NMIBC, cystectomy can

be potentially curative. It is uncertain whether new therapies by delaying potentially curative cystectomy risk loss of cure.

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This is the first ICER review of treatments for non-muscle invasive bladder cancer.

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Appendix A. Search Strategic Results

Table A1. PRISMA 2009 Checklist

		Checklist Items
TITLE		
Title	1	Identify the report as a systematic review, meta-analysis, or both.
ABSTRACT		
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.
INTRODUCTION		
Rationale	3	Describe the rationale for the review in the context of what is already known.
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).
METHODS		
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).

		Checklist Items
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I2) for each meta-analysis.
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.
RESULTS		
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).
DISCUSSION		
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., health care providers, users, and policy makers).
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.
FUNDING		
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.

From: Moher D, Liberati A, Tetzlaff J, Altman DG. The PRISMA Group (2010). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *Int J Surg*. 2010;8(8):658. doi:10.1016/j.ijsu.2010.02.007[48]

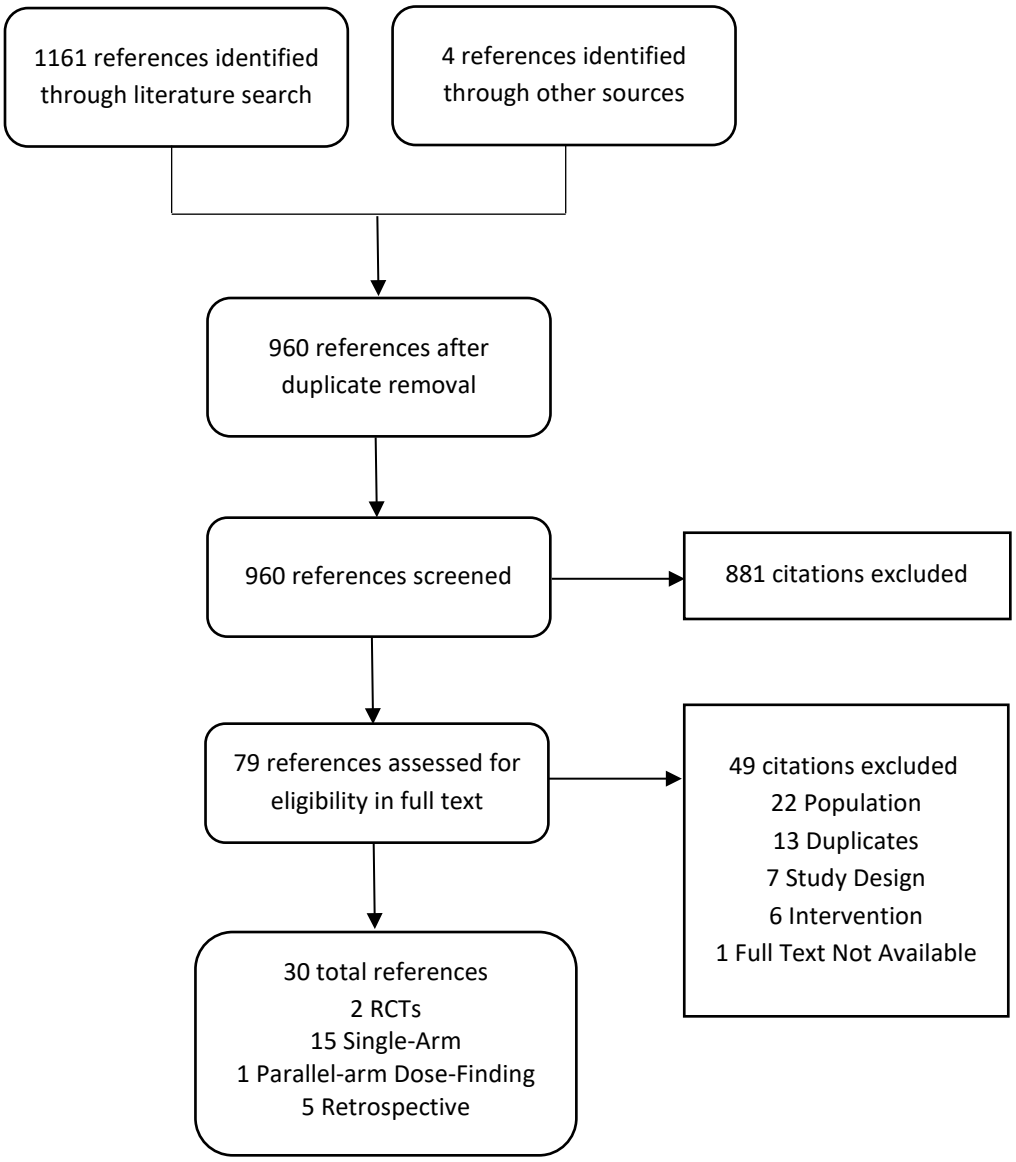
Table A2. Search Strategy of Ovid MEDLINE® Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE® Daily, Ovid MEDLINE and Versions® 1946 to Present

1	Urinary Bladder neoplasms/ or bladder tumor/
2	((urothelial or urothelium) adj3 (cancer* or carcin* or malig* or tumor* or tumour* or neoplas*)).ti,ab
3	1 OR 2
4	(non-muscle invasive bladder cancer or non-muscle invasive bladder cancer or nonmuscle invasive bladder cancer or nonmuscle-invasive bladder cancer or non-muscle-invasive bladder cancer or NMIBC or transitional cell carcinoma or transitional-cell carcinoma of the bladder).ti,ab
5	(((Ta or T a or T1 or T 1 or TIS) adj5 (cancer* or carcin* or malig* or tumor* or tumour* or neoplas*)) or (papillary adj5 (disease* or tumor* or tumour* or cancer* or carcin* or malig* or neoplas*))).ti,ab.
6	(carcinoma in situ or CIS).ti,ab or exp carcinoma in situ/
7	4 OR 5 OR 6
8	3 AND 7
9	(Nadofaragene Firadenovec OR Adstiladrin OR Instiladrin OR rAd-IFN OR rAd-IFNa OR Syn3 OR SCH 72105 OR SCH-721015 OR SCH721015).ti,ab
10	(Oportuzumab monatox OR VB4-845 OR VB4 845 OR VB4845 OR Vicinium).ti,ab
11	Pembrolizumab/ OR (Keytruda OR Pembrolizumab OR MK-3475 OR MK3475 OR MK 3475).ti,ab
12	Gemcitabine/ OR (Gemcitabine OR Gemzar Or LY-188011 Or LY 188011 Or LY188011).ti,ab
13	Docetaxel/ Or (Docetaxel Or Taxotere Or Docefrez OR RP56976 OR RP-56976 OR RP 56976).ti,ab
14	11 OR 12 OR 13 OR 14 OR 15
15	8 AND 14
16	(addresses or autobiography or bibliography or biography or clinical trial, phase I or comment or congresses or consensus development conference or duplicate publication or editorial or guideline or in vitro or interview or lecture or legal cases or legislation or letter or news or newspaper article or patient education handout or periodical index or personal narratives or portraits or practice guideline or review or video audio media).pt.
17	15 NOT 16
18	(exp animals/ or exp animal/ or exp nonhuman/ or exp animal experiment/ or animal model/ or animal tissue/ or non human/ or (rat or rats or mice or mouse or swine or porcine or murine or sheep or lambs or pigs or piglets or rabbit or rabbits or cat or cats or dog or dogs or cattle or bovine or monkey or monkeys or trout or marmoset$1 or basic research or cell lines or in vitro or animal model or canine).tw.) not (humans/ or human/ or human experiment/ or (human* or men or women or patients or subjects).tw.)
19	17 NOT 18
20	Limit 19 to English Language
Last Search: October 13, 2020	

Table A3. Search Strategy of EMBASE SEARCH

#1	'bladder tumor'/exp OR 'transitional cell carcinoma'/exp OR 'non muscle invasive bladder cancer'/exp
#2	((urothelial OR urothelium) NEAR/3 (cancer* OR carcin* OR malig* OR tumor* OR tumour* OR neoplas*)):ti,ab
#3	#1 OR #2
#4	'non muscle invasive bladder cancer':ti,ab OR 'non-muscle invasive bladder cancer':ti,ab OR NMIBC:ti,ab OR 'nonmuscle invasive bladder cancer':ti,ab OR 'non-muscle-invasive bladder cancer':ti,ab OR 'nonmuscle-invasive bladder cancer':ti,ab OR 'transitional cell carcinoma':ti,ab OR 'transitional-cell carcinoma of the bladder':ti,ab
#5	(((ta:ti,ab OR t:ti,ab) AND a:ti,ab OR t1:ti,ab OR t:ti,ab) AND 1:ti,ab OR tis:ti,ab) AND (cancer*:ti,ab OR carcin*:ti,ab OR malig*:ti,ab OR tumor*:ti,ab OR tumour*:ti,ab OR neoplas*:ti,ab)
#6	'papillary':ti,ab AND (disease*:ti,ab OR tumor*:ti,ab OR tumour*:ti,ab OR cancer*:ti,ab OR carcin*:ti,ab OR malig*:ti,ab OR neoplas*:ti,ab)
#7	'carcinoma in situ':ti,ab OR 'cis':ti,ab OR 'carcinoma in situ'/exp
#8	#4 OR #5 OR #6 OR #7
#9	#3 AND #8
#10	'nadofaragene firadenovec':ti,ab OR 'adstiladrin':ti,ab OR 'instiladrin':ti,ab OR 'rad-ifn':ti,ab OR 'rad-ifna':ti,ab OR 'syn3':ti,ab OR 'sch 72105':ti,ab OR 'sch-721015':ti,ab OR 'sch721015':ti,ab
#11	'oportuzumab monatox':ti,ab OR 'vb4-845':ti,ab OR 'vb4 845':ti,ab OR 'vb4845':ti,ab OR 'Vicinium':ti,ab
#12	'pembrolizumab'/exp OR 'keytruda':ti,ab OR 'pembrolizumab':ti,ab OR 'mk-3475':ti,ab OR 'mk3475':ti,ab OR 'mk 3475':ti,ab
#13	'gemcitabine'/exp OR 'gemcitabine':ti,ab OR 'gemzar':ti,ab OR 'ly 188011':ti,ab OR 'ly188011':ti,ab
#14	'docetaxel'/exp OR 'docetaxel':ti,ab OR 'taxotere':ti,ab OR 'docefrez':ti,ab OR 'rp56976':ti,ab OR 'rp-56976':ti,ab OR 'rp 56976':ti,ab
#15	#10 OR #11 OR #12 OR #13 OR #14
#16	#9 AND #15
#17	'chapter'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it OR 'review'/it OR 'short survey'/it
#18	#16 Not #17
#19	('animal'/exp OR 'nonhuman'/exp OR 'animal experiment'/exp) NOT 'human'/exp
#20	#18 NOT #19
#21	#20 AND [english]/lim
Last Search: October 13, 2020	

Figure A1. PRISMA flow Chart Showing Results of Literature Search for Non-Muscle Invasive Bladder Cancer



RCT: randomized controlled trial

Appendix B. Previous Systematic Reviews and Technology Assessments

We were unable to identify any health technology assessments (HTAs) of nadofaragene firadenovec (Adstiladrin®), oportuzumab monatox (Vicineum®), intravesical therapy with gemcitabine ± docetaxel, and systemic pembrolizumab specifically for NMIBC from NICE or CADTH. We summarized systematic reviews of therapies for NMIBC.

Li R, Sundi D, Zhang J, et al. Systematic Review of the Therapeutic Efficacy of Bladder-preserving Treatments for Non-muscle-invasive Bladder Cancer Following Intravesical Bacillus Calmette-Guérin [published online ahead of print, 2020 Mar 3]. ***Eur Urol*****. 2020;S0302-2838(20)30118-4. doi:10.1016/j.eururo.2020.02.012**

This systematic review was performed to examine response and reoccurrence rates associated with bladder-sparing agents used to treat BCG-unresponsive NMIBC. Forty-two prospective clinical trials were included examining oportuzumab monatox, pembrolizumab, gemcitabine, valrubicin, docetaxel, and nadofaragene firadenovec among other therapy options. The primary outcomes were complete response rate (CRR), recurrence-free rate (RFR), and/or disease-free rate (DFR), which indicate lack of tumor or recurrence; CRR was reported in studies with CIS patients, RFR was used in studies examining patients with papillary disease, and DFR was reported in studies with patient having combination of CIS and papillary disease. The secondary outcomes included progression-free rate (PFR) and toxicity.

In the studies of patients with CIS, the median CRR was 43% (range: 15-58%, n=6) at three months, 26% (range: 18-44%, n=5) at six months, 17% (range: 9-31%, n=6) at twelve months, 22% (range: 22%, n=1) at eighteen months, and 8% (range: 4-11%, n=2) at twenty-four months. The median RFR in the trials of patients with papillary disease were 88% (range: 80-95%, n=2) at three months, 67% (range: 60-95%, n=3) at six months, 44% (range: 10-78%, n=3) at twelve months, 36% (range: 10-70%, n=4) at eighteen months, and 10% (range: 5-70%, n=3) at twenty-four months. Lastly, the median DRF, from the trials of patients with both CIS and papillary disease, was 51% (range: 28-99%, n=14) at three months, 43% (range: 8-73%, n=9) at six months, 29% (range: 6-88%, n=13) at twelve months, 40% (range: 29-40%, n=3) at eighteen months, and 27% (range: 6-62%, n=9) at twenty-four months.

Of the study arms involving immunomodulatory agents (IFNα, Adstiladrin, etc.) in patients with CIS and/or papillary, the median DFR was 49% (range: 29-69%, n=4) at three months, 41% (range: 14-47%, n=5) at six months, 29% (range: 6-35%, n=5) at twelve months. Furthermore, the resulting CRRs of treatment with cytotoxic (gemcitabine, docetaxel, etc.) were 44% (range: 36-58%, n=5) at three months, 26% (range: 18-44%, n=5) at six months, 17% (range: 9-31%, n=6) at twelve months.

The median PFR was 91% (range: 61-99%) and 23 dose-limiting toxicities (DLT) occurred out of 2,046 patients.

The authors were unable to conduct a formal statistical comparison due to inconsistencies in reporting and study design as well as complex therapy schedules and biological heterogeneities. Despite these limitations, the authors conclude bladder-sparing therapies provide modest efficacy in patients with BCG-unresponsive NMIBC.

Kamat AM, Lerner SP, O'Donnell M, et al. Evidence-based Assessment of Current and Emerging Bladder-sparing Therapies for Non-muscle-invasive Bladder Cancer After Bacillus Calmette-Guerin Therapy: A Systematic Review and Meta-analysis [published online ahead of print, 2020 Mar 19]. ***Eur Urol Oncol*****. 2020;S2588-9311(20)30031-6. doi:10.1016/j.euo.2020.02.006**

This systematic review and meta-analysis of thirty trials evaluated the safety and efficacy of current and emergent therapies for the treatment of NMIBC in patients who fail BCG therapy. In the groups with two or more prior BCG courses, the estimated complete response CR/relapse-free survival (RFS)/disease-free survival (DFS) rates were highest with paclitaxel-hyaluronic acid (73%) and nadofaragene firadenovec (68%) at three months. The pooled estimated CR/RFS/DFS rate was 46% (95% CI: 38% to 54%) at three months, 38% (95% CI: 31% to 45%) at six months, and 24% (95% CI: 16% to 32%) at twelve months. In the group with one or more prior BCG course, the pooled estimated CR/RFS/DFS rate was 60% (95% CI: 45% to 74%) at three months, 49% (95% CI: 35% to 63%) at six-months, and 36% (95% CI: 25% to 47%) at twelve months.

Further analysis showed studies in patients with one or more prior BCG course and greater than half (≥50%) of patients with CIS had lower therapy response rates than studies with less than half (<50%) of patients with CIS. The researchers acknowledged the limitations of inconsistencies between the studies in safety and efficacy outcomes, which may have impacted the results of this systematic review and meta-analysis. The number of previous BCG courses and proportion of patients with CIS varied widely between included studies. Lastly, this study was not registered with the International Prospective Register of Systematic Reviews (PROSPERO).

Jones G, Cleves A, Wilt TJ, Mason M, Kynaston HG, Shelley M. Intravesical gemcitabine for non-muscle invasive bladder cancer. ***Cochrane Database of Systematic Reviews*** **2012;1;CD009294. doi: 10.1002/14651858.CD009294.pub2.**

A systematic review was conducted to evaluate the effectiveness and toxicity of intravesical gemcitabine in preventing tumor recurrence and progression in (NMIBC). The primary outcome was treatment efficacy, measured by reoccurrence or recurrence-free survival; secondary outcomes included disease progression, overall survival, disease-specific survival, quality of life, and side-effects.

Six prospective, randomized trials examining intravesical gemcitabine treatment in NMIBC, but only two had patient populations with NMIBC refractory to BCG therapy. One study found intravesical gemcitabine was superior to BCG in reducing and delaying tumor reoccurrence among patients with high-risk NMIBC refractory to BCG therapy. The other study found that the efficacy and toxicity profile of gemcitabine was favorable compared to mitomycin in patients with recurrent transitional cell carcinoma stages Ta or T1, Grades 1-3 who had progressed or relapsed after intravesical BCG therapy.

Therefore, in terms of BCG-refractory patients, this systematic review concluded that intravesical gemcitabine may have a role in treating NMIBC patients, especially as an alternative to mitomycin C. The strict trial inclusion criteria may have limited the author's identification of relevant studies, such as non-randomized control trial designs and retrospective data.

Rutherford C, Patel MI, Tait MA, et al. Patient-reported outcomes in non-muscle invasive bladder cancer: a mixed-methods systematic review [published online ahead of print, 2020 Sep 22]. *Qual Life Res*. 2020;10.1007/s11136-020-02637-9. doi:10.1007/s11136-020-02637-9

This systematic review aimed to synthesize key patient-reported outcomes (PRO) in the non-muscle invasive bladder cancer (NMIBC) treatment space to understand treatment pathways and differences among available treatment options. A search conducted in six databases identified 3193 references, and 29 of these studies fit the eligibility criteria. This included 10 RCTs, 10 cohort studies, eight cross-sectional studies and one qualitative study with enrolling a varied sample population from acute, community, and long-term care settings in Europe, the United Sates, Asia, Canada, and Australia. Narrative synthesis was used to interpret PRO evidence for 3 main categories: within group differences over time to understand disease trajectory, differences between disease statin and treatment groups, and comparisons of PRO findings between end of induction treatment and end of maintenance treatment periods to understand symptom burden patterns (e.g. burden worsens, stabilizes, or reduces).

Across the 29 included studies, the most reported symptoms both during and after treatment were pain in bladder area, urinary frequency and urgency, and burning while urinating. PROs were not seen to be worse during maintenance as compared to induction, with the exception in potentially role and cognitive function, as well as nausea and appetite loss. There was no observed difference in PROs with more frequent instillations of a treatment in many of the studies. Lastly, the studies that assessed PROs with more generic measures identified no within or between group differences whereas studies that used bladder cancer or symptom specific measures identified some differences.

The importance of PRO data is highlighted in this review as it aides key decision making discussions between clinicians and patients on topics such as potential treatment effects and patient preference. The review concluded with treatments available for NMIBC leading a host of factors impacting a patients' health-related quality of life, there is a strong need for additional PRO studies to better understand the patient experience across treatment trajectories.

Appendix C. Ongoing Studies

Table C1. Ongoing Studies

Title/Trial Sponsor	Study Design	Treatment Arms	Patient Population	Primary Outcomes	Estimated Completion Date
A Phase III, Open Label Study to Evaluate the Safety and Efficacy of INSTILADRIN® (rAd-IFN)/Syn3) Administered Intravesically to Patients with High Grade, BCG Unresponsive Non-Muscle Invasive Bladder Cancer (NMIBC) FKD Therapies Oy In collaboration with Society of Urologic Oncology Clinical Trials Consortium NCT02773849	Phase III clinical trial, single arm Enrollment: 157 Duration: 48 months	Single Arm: Intravesical administration of Instiladrin into bladder	Inclusion Criteria: • Age: ≥ 18 years • Confirmed CIS only, Ta/T1 high-grade disease with concomitant CIS, or Ta/T1 high-grade disease without concomitant CIS; • BCG-unresponsive (high-grade NMIBC with persistent disease or relapse of disease within 12 months of BCG treatment) Exclusion Criteria: Current or previous evidence of muscle invasive or metastatic disease Current systemic therapy for bladder cancer Current or prior pelvic external beam radiotherapy within 5 years Prior treatment with adenovirus-based drugs; Suspected hypersensitivity to IFN alfa2b Intravesical therapy within 8 weeks prior to beginning study treatment	Primary Outcome: • Complete response rate (CRR) at 12 months in patients with Carcinoma in situ (CIS), with or without concomitant high-grade Ta or T1 papillary disease, measured by the number of patients without recurrence of high-grade disease using results from urine cytology, cystoscopy, and biopsy of the bladder. Secondary Outcomes: • Durability of complete response in patients with CIS (with or without concomitant Ta or T1 papillary disease) achieving complete response up to 48 months • Event-free survival and durability of event-free survival of patients with high-grade Ta or T1 papillary disease (without concomitant CIS), up to 48 months • Incidence of and time to cystectomy in the study at 48 months • Overall incidence of and time to survival in all patients at 48 months • Anti-adenoviral antibody levels for correlation to response rate • Safety of INSTILADRIN, evaluated with type, incidence, relatedness and severity of treatment emergent adverse events over 48 months • Durability of response during the long term follow up period at 48 months	August 31, 2022

Title/Trial Sponsor	Study Design	Treatment Arms	Patient Population	Primary Outcomes	Estimated Completion Date
Phase III VISTA Sponsor: Viventia Bio (Sesen Bio) NCT02449239	Open-label, single-arm, multicenter Enrollment: Duration: Up to 104 weeks	Induction: 30 mg Vicineum instilled for 2 hours twice weekly for 6 weeks followed by once weekly for 6 weeks, for a total of 12 weeks Maintenance: 30 mg Vicineum once weekly or every other week for up to 104 weeks	Inclusion Criteria: • Histologically confirmed non muscle-invasive urothelial carcinoma including CIS, T1 or high-grade Ta papillary disease • Cohort 1: Subjects with CIS ± associated papillary disease whose disease is determined to be refractory or relapsed within 6 months of the last dose of adequate BCG treatment • Cohort 2: Subjects with CIS ± associated papillary disease whose disease is determined to be refractory or relapsed more than 6 months but within 11 months of the last dose of adequate BCG treatment • Cohort 3: Subjects with high-grade Ta or any grade T1 papillary disease (without CIS) whose disease is determined to be refractory or relapsed	Primary Outcome: • Complete response rate in patients with CIS with or without resected papillary disease following initiation of Vicineum therapy up to 24 months Secondary Outcomes: • Recurrence Rate • Event-free survival • Number of patients with adverse events as a measure of tolerability • Changes in Vital Signs • Time to cystectomy • Time to progression • Progression-free survival	Nov 2021

Title/Trial Sponsor	Study Design	Treatment Arms	Patient Population	Primary Outcomes	Estimated Completion Date
			within 6 months of the last dose of adequate BCG treatment Exclusion Criteria: • Evidence of urethral or upper tract TCC within past 2 years • Any intravesicular or other chemotherapy treatment within 2 weeks or any investigational agent within 4 weeks prior to initial study dose		
A Phase II Clinical Trial to Study the Efficacy and Safety of Pembrolizumab (MK-3475) in Subjects with High Risk Non-Muscle Invasive Bladder Cancer (NMIBC) Unresponsive to Bacillus Calmette-Guerin (BCG) Therapy [MK-3475-057/KEYNOTE-057] Merck Sharp & Dohme Corp. NCT02625961	Phase II clinical trial, single arm, Enrollment: 260 Duration: 3 years	Arm 1: Pembrolizumab 200 mg intravenously every 3 weeks for up to 24 months	Inclusion Criteria: • 18+ years old with histologically-confirmed diagnosis of high risk non-muscle-invasive (T1, high grade Ta and/or CIS TCC of the bladder • Fully resected disease at study entry • BCG-unresponsive high-risk NMIBC after treatment with adequate BCG therapy • Ineligible for or refusal of radical cystectomy Exclusion criteria: • Muscle-invasive, locally advanced nonresectable, or metastatic urothelial carcinoma (i.e., T2, T3, T4, and/or stage IV)	Primary Outcomes: • Complete response rate up to 3 years • Disease free survival (up to 3 years) Secondary Outcomes: • Duration of response up to 3 years	July 30, 2023

Title/Trial Sponsor	Study Design	Treatment Arms	Patient Population	Primary Outcomes	Estimated Completion Date
			• Concurrent extra-vesical non-muscle invasive TCC of the urothelium • Previously received an investigational therapy or device within 4 weeks • Received intravesical chemotherapy or immunotherapy after cystoscopy/TURBT • Received prior small molecule chemotherapy or radiation 2 weeks • Prior anti-programmed cell death 1 (PD-1), anti-PD-ligand 2 (L2), or co-inhibitory T-cell receptor therapy • History of allogeneic tissue/solid organ transplant		
A Phase 3, Randomized, Comparator-controlled Clinical Trial to Study the Efficacy and Safety of Pembrolizumab (MK-3475) in Combination With Bacillus Calmette-Guerin (BCG) in Participants With High-risk Non-muscle Invasive Bladder Cancer	Phase 3, randomized, comparator-controlled, open-label Enrollment: 550 Duration: 5 years	Arm 1 (experimental): BCG (induction and maintenance) + Pembrolizumab (200 mg IV every 2 weeks for 35 doses) Arm 2 (control): BCG (induction and maintenance) monotherapy	<u>Inclusion Criteria:</u> • Histologically-confirmed diagnosis of non-muscle invasive (T1, high grade Ta and/or CIS) TCC of the bladder • Treated with one adequate course of BCG induction therapy for the treatment of HR NMIBC and has persistent or recurrent HR NMIBC • Undergone cystoscopy/ TURBT to remove all resectable disease	<u>Primary Outcome Measure:</u> • Complete Response Rate (CRR), up to 3.5 years <u>Secondary Outcome Measures:</u> • Event-Free Survival (EFS), up to 5 years • Recurrence-Free Survival (RFS), up to 5 years • Overall Survival (OS), up to 5 years • Disease Specific Survival (DSS), up to 5 years • Time to Cystectomy up to 5 years • 12-Month EFS Rate • Duration of Response (DOR), up to 5 years • 12-Month DOR Rate • Percentage of Participants Experiencing AEs	November 25, 2024

Title/Trial Sponsor	Study Design	Treatment Arms	Patient Population	Primary Outcomes	Estimated Completion Date
(HR NMIBC) that is Persistent or Recurrent Following BCG Induction (MK-3475-676/KEYNOTE-676) Merck Sharp & Dohme Corp. NCT03711032			Exclusion Criteria: • Persistent T1 disease following an induction course of BCG • History of or concurrent muscle invasive (i.e., T2, T3, T4), locally advanced non-resectable or metastatic UC • Concurrent extra-vesical non-muscle invasive TCC of the urothelium, concurrent upper tract involvement, or invasive prostatic TCC including T1 or greater disease, or ductal invasion • Received prior therapy with anti-PD-1, anti-PD-L1, or anti-PD-L2 agent or with an agent directed to another co-inhibitory T-cell receptor • Received prior systemic anti-cancer therapy including investigational agents within 4 weeks of start of study	• Percentage of Participants Discontinuing Study Drug Due to AEs • Change from Baseline in the EORTC- QLQ-C30 Global Health Status/Quality of Life (Items 29 and 30) Combined Score • Change from Baseline in EORTC QLQ-C30 Physical Functioning (Items 1-5) Combined Score • Change from Baseline in EORTC QLQ-Non-muscle Invasive Bladder Cancer Module 24 (NMIBC24) Total Score • Change from Baseline in European Quality of Life (EuroQoL)-5 Dimensions, 5-level Questionnaire (EQ-5D-5L) Visual Analogue Score (VAS)	

AE: adverse event, BCG: bacillus calmette guerin, CIS: carcinoma in situ, ECOG: eastern cooperative oncology group, EORTC: European Organization for Research and Treatment of Cancer, HR: high-risk, NMIBC: non muscle invasive bladder cancer, QLQ-C30: Quality of Life Questionnaire-Core 30 rAd-IFN/Syn3: recombinant adenovirus delivered inferferon alpha 2-b with Syn3, Ta: non-invasive papillary tumor, T1: tumor invading subepithelial connective tissue, TURBT: trans urethral resection of bladder tumor

Source: www.ClinicalTrials.gov (NOTE: studies listed on site include both clinical trials and observational studies)

Appendix D. Comparative Clinical Effectiveness Supplemental Information

We performed screening at both the abstract and full-text level. A single investigator screened all abstracts identified through electronic searches according to the inclusion and exclusion criteria described earlier. We did not exclude any study at abstract-level screening due to insufficient information. For example, an abstract that did not report an outcome of interest would be accepted for further review in full text. We retrieved the citations that were accepted during abstract-level screening for full text appraisal. One investigator reviewed full papers and provided justification for exclusion of each excluded study.

We also included FDA documents related to pembrolizumab. These included the manufacturer's submission to the agency and internal FDA review documents. All literature that did not undergo a formal peer review process is described separately. Because all included trials were single arm, non-comparative studies, we did not assign them a quality rating.

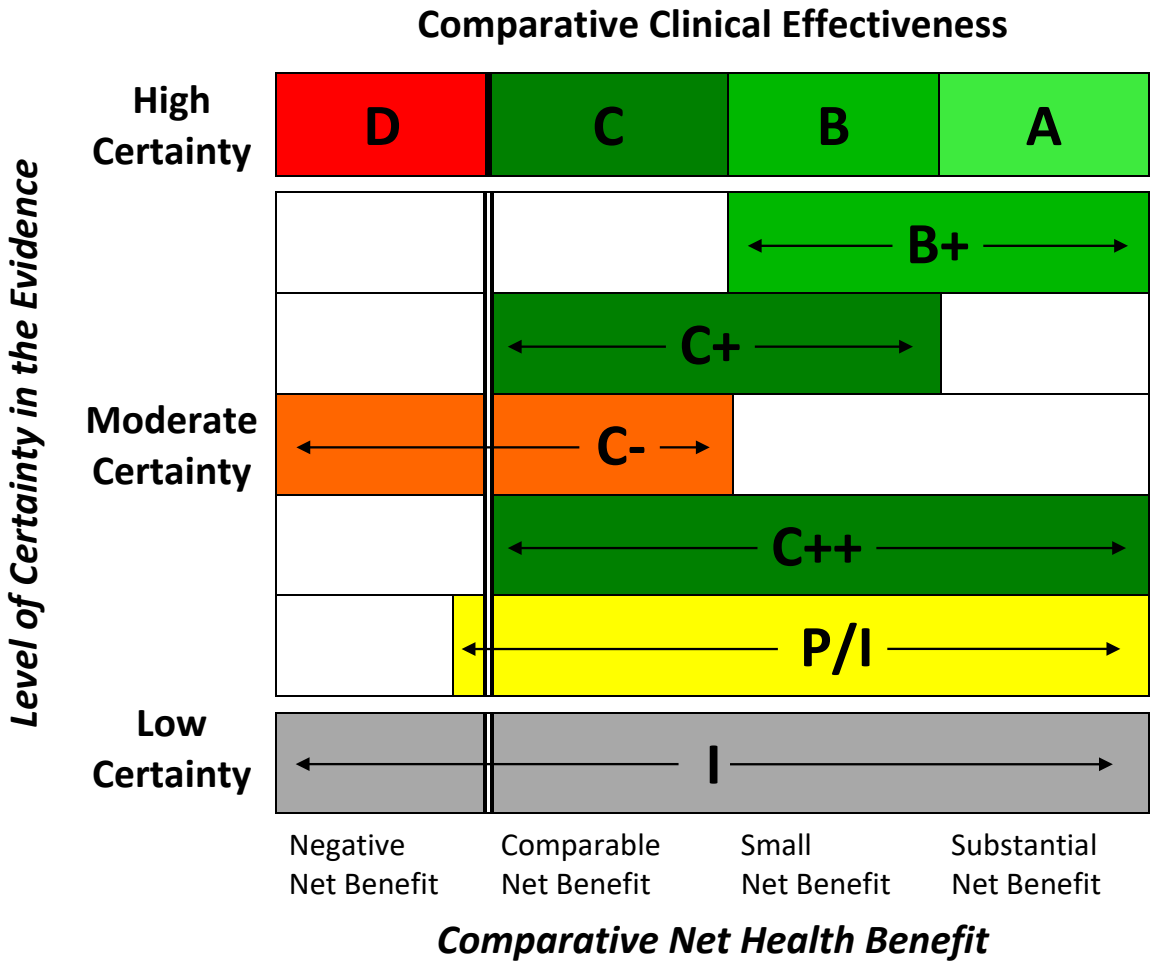
ICER Evidence Rating

We used the ICER Evidence Rating Matrix (see Figure D1) to evaluate the evidence for a variety of outcomes. The evidence rating reflects a joint judgment of two critical components:

1. The magnitude of the difference between a therapeutic agent and its comparator in "net health benefit" – the balance between clinical benefits and risks and/or adverse effects; and

2. The level of certainty in the best point estimate of net health benefit.[49,116]

Figure D1. ICER Evidence Rating Matrix



A = "Superior" - *High certainty of a substantial (moderate-large) net health benefit*
B = "Incremental" - *High certainty of a small net health benefit*
C = "Comparable"- *High certainty of a comparable net health benefit*
D= "Negative"- *High certainty of an inferior net health benefit*
B+= "Incremental or Better" – *Moderate certainty of a small or substantial net health benefit, with high certainty of at least a small net health benefit*
C+ = "Comparable or Incremental" - *Moderate certainty of a comparable or small net health benefit, with high certainty of at least a comparable net health benefit*
C- = "Comparable or Inferior" *– Moderate certainty that the net health benefit is either comparable or inferior with high certainty of at best a comparable net health benefit*
C++ = "Comparable or Better" - *Moderate certainty of a comparable, small, or substantial net health benefit, with high certainty of at least a comparable net health benefit*
P/I = "Promising but Inconclusive" *- Moderate certainty of a small or substantial net health benefit, small likelihood of a negative net health benefit*
I = "Insufficient" – *Any situation in which the level of certainty in the evidence is low*

Table D1. Study Design

Trial Details	Design and Duration of Follow-up	Population, Total N	Interventions and Dosing Procedures	Inclusion / Exclusion Criteria
Nadofaragene Firadenovec				
Phase III[19] NCT02773849 Sponsor: FKD Therapies Collaborator: Society of Urologic Oncology Clinical Trials Consortium Estimated Completion: August 2022	Open-label study • 12-month treatment period • Up to 36 months of follow up • Loss to follow up: n=4	18+ years BCG-unresponsive NMIBC with either: • Carcinoma in situ (CIS) only • Ta/T1 high-grade disease ± concomitant CIS N=157 (safety population)	rAd-IFN/Syn3 (intravesical administration) 3 x 10^{11} vps/mL every 3 months up to 4 instillations	**Inclusions** • 18+ years old with BCG unresponsive NMIBC with either CIS only or Ta/T1 high-grade disease ± concomitant CIS • Have received at least 2 previous courses of BCG within a 12-month period (at least 5 or 6 induction BCG instillations and at least 2 out of 3 instillations of maintenance BCG, or at least two of six instillations of a second induction course, where maintenance BCG is not given) • At time of tumor recurrence, patients with CIS alone or high-grade Ta/T1 with CIS should be within 12 months of last exposure to BCG and those without CIS should be within 6 months • All visible papillary tumors must be resected and those with persistent T1 on TURBT should undergo additional re-TURBT 14-60 days prior to study **Exclusions** • Current or previous evidence of muscle invasive or metastatic disease • Current systemic therapy for bladder cancer • Prior treatment with adenovirus-based drugs • Previous intravesical BCG therapy, which can be given at least 5 weeks before the diagnostic biopsy required for entry • Patients with T1 disease accompanied by

Trial Details	Design and Duration of Follow-up	Population, Total N	Interventions and Dosing Procedures	Inclusion / Exclusion Criteria
				presence of hydronephrosis secondary to primary tumor
Phase II SUO-CTC[50] NCT01687244 Sponsor: FKD Therapies Completion Date: Feb 2016	Phase II, randomized, open-label, parallel arm Multicenter: 13 centers in the U.S. between November 2012 and April 2015 • 12-months treatment period • Patients without recurrence of HG disease at months 3, 6, and 9 were then retreated at months 4, 7, and 10 • Final efficacy evaluation at month 12 • All patients monitored in 3-year follow-up period • Loss to follow up: n=3	18+ years old with high-grade BCG-refractory or relapsed NMIBC • Ta or T1 alone • CIS alone • CIS ± papillary disease. N=40	• rAd-IFN: Dose $1x10^{11}$ vps/mL in 75mL (low-dose) Total Dose: $7.5x10^{12}$ vp • rAd-IFN: Dose $3x10^{11}$ vps/mL in 75mL (high-dose) Total Dose: $2.25x10^{13}$ vp (every 3 months up to 4 instillations)	**Inclusions** • Aged 18 years or older with high-grade BCG refractory or relapsed NMIBC including: high-grade non-invasive papillary carcinomas (Ta) and subjects with high grade tumors that invade sub-epithelial connection tissue (T1) or carcinoma in situ only or CIS ± Ta or T1 • Complete resection of visible papillary lesions or CIS by TURBT or endoscopic resection between 14 and 60 days prior study treatment • Life expectancy > 2 years in opinion of investigator • ECOG status 2 or less **Exclusions** • Current or previous evidence of muscle invasive or metastatic disease • Current systemic therapy for bladder cancer • Current or prior pelvic external beam radiotherapy • Prior treatment with adenovirus-based drugs • Suspected hypersensitivity to interferon alpha • Existing urinary tract infection or bacterial cystitis • Subjects who cannot hold instillation for 1 hour or cannot tolerate intravesical dosing or intravesical surgical manipulation • Intravesical therapy within 6 weeks of enrollment

Trial Details	Design and Duration of Follow-up	Population, Total N	Interventions and Dosing Procedures	Inclusion / Exclusion Criteria
Phase I **Dinney 2013[51]** NCT: unknown / unregistered Sponsor: unknown Completion Date: Sep 2013	Phase I, non-randomized, open-label, dose-escalating, multicenter trial • A single treatment as administered • Safety was evaluated for ≥ 12 weeks • Lost to follow up: n=1	Patients 18 years or older with histologically confirmed urothelial NMIBC (Ta, Tis, or T1) N=17	At least 3 patients were assigned to one of five dosing cohorts, using a standard Phase 1 dose-escalation design (3×10^9 to 3×10^{11} particles/mL of rAd-IFN, Syn3 1 mg/mL in all patients; total volume 75mL; dwell time 1 hour).	**Inclusions** • Patients 18 years or older with histologically confirmed urothelial NMIBC (Ta, Tis, or T1) • Patients were required to have histologically proven disease recurrence after at least 2 cycles of BCG, with or without recombinant IFNα protein, and a minimum of 3 months since last treatment. • Patients who received a second 6-week induction course were also eligible **Exclusions** • Patients with T1 disease were not enrolled unless they explicitly declined cystectomy despite managing physician recommendation • Patients with psychiatric conditions, significant cardiovascular or pulmonary disease, uncontrolled diabetes, or immune diseases were excluded • Previous intravesical gene therapy
Oportuzumab Monatox				
Phase III VISTA[52] NCT02449239 Sponsor: Viventia Bio (Sesen Bio) Estimated Completion: Nov 2021	Open-label, single arm, multicenter • 12-week induction phase • Maintenance Phase: up to 21 monthly cycles •Total treatment period: up to 104 weeks	18+ years old with BCG-unresponsive NMIBC with either: • any grade T1 papillary disease • high-grade Ta papillary disease • CIS ± papillary disease N=133	Induction: 30 mg Vicineum instilled for 2 hours twice weekly for 6 weeks followed by once weekly for 6 weeks, for a total of 12 weeks Maintenance: 30 mg Vicineum once weekly or every other week for up to 104 weeks	**Inclusions** • Histologically confirmed non muscle-invasive urothelial carcinoma including CIS, T1 or high-grade Ta papillary disease • Cohort 1: Subjects with CIS ± associated papillary disease whose disease is determined to be refractory or relapsed within 6 months of the last dose of adequate BCG treatment • Cohort 2: Subjects with CIS ± associated papillary disease whose disease is determined to be refractory or relapsed more than 6 months but within 11 months of

Trial Details	Design and Duration of Follow-up	Population, Total N	Interventions and Dosing Procedures	Inclusion / Exclusion Criteria
				the last dose of adequate BCG treatment • Cohort 3: Subjects with high-grade Ta or any grade T1 papillary disease (without CIS) whose disease is determined to be refractory or relapsed within 6 months of the last dose of adequate BCG treatment **Exclusions** • Evidence of urethral or upper tract transitional cell carcinoma within past 2 years • Patients with hydronephrosis • Any intravesicular or other chemotherapy treatment within 2 weeks or any investigational agent within 4 weeks prior to initial study dose • Active, uncontrolled impairment of the urogenital, renal, hepatobiliary, cardiovascular, gastrointestinal, neurologic or hematopoietic systems which would predispose patients to development of complications • Diagnosis of another malignancy within 2 years before the first dose of study treatment
Phase II - 02 -IIA **Kowalski 2012[53]** NCT00462488 Sponsor: Viventia Bio (Sesen Bio)	Open-Label, multicenter, 2-arm trial with a single stage design Multicenter: 21 sites in North America (Mar 2007-July 2008)	18+ years old with BCG refractory/intolerant TCC of the bladder and residual CIS ± concurrent Ta or T1 tumors N=45	30 mg intravesical Vicineum in 40 mL sterile saline; instilled into bladder retained for two hours, then voided (Induction and	**Inclusions** • 18 years of age or older with histologically-confirmed TCC of the bladder. • Histologically-confirmed CIS, with or without non-invasive papillary disease • Immunohistochemically-confirmed EpCAM positive disease. • Patient must have a life expectancy of at least 12

Trial Details	Design and Duration of Follow-up	Population, Total N	Interventions and Dosing Procedures	Inclusion / Exclusion Criteria
Completion Date: Oct 2009	• Cohort 1: 12-week induction with potential to move either into a second induction phase or first maintenance phase • Cohort 2: 13-week induction, 12 week maintenance phase • Up to 3 maintenance cycles • Follow-up: up to 1 year • Loss to follow-up: n=0		Maintenance dosing regimens varies between cohorts - see full text for diagram)	months. • Patient must have, within the last 24 months, failed to respond to at least 1 cycle of treatment with BCG (with or without interferon) or be intolerant to BCG treatment. • Patient must have had a TURBT mapping the location of tumour and quantifying the area of bladder affected. • Must have documented residual CIS (i.e., unresectable disease) prior to study drug administration. **Exclusions** • Has evidence of urethral or upper TCC by biopsy or upper tract radiological imaging (i.e. intravenous pyelogram, computed tomography (CT) urogram, or retrograde pyelogram) within the past 2 years • Prior intravesical chemotherapy or investigational or anti-cancer treatments within the last 2 months, inclusive of single-dose adjuvant intravesical chemotherapy immediately post-TURBT • Existing severe urinary tract infection or recurrent severe bacterial cystitis
Phase I **Kowalski 2010[54]** NCT: unknown / unregistered Sponsor: unknown Completion Date: 2010	Phase I, open-label, multicenter, dose-escalating trial • Weekly instillations for 6 consecutive weeks with ascending doses from 0.1 to 30.16 mg • Patients followed for 4-6 weeks post-therapy without treatment	18+ years old with BCG refractory/intolerant NMIBC with either Ta, T1, in situ carcinoma [TIS] N=64	Eight dose levels were initially evaluated, starting at 0.1 mg once weekly for 6 consecutive weeks and escalating through 0.2, 0.33, 0.66, 1.32, 2.64, 5.28, and 10.56 mg/dose. The maximum tolerated dose was not	**Inclusions** • Patients 18 years of age or older with immunohistochemically confirmed EpCAM-positive Grade 2 or 3 NMIBC (Ta, T1, TIS), either refractory to (recurrence within 2 years following at least one complete cycle of BCG therapy) or intolerant of BCG therapy • Adequate renal, hepatic, and hematological function **Exclusions**

Trial Details	Design and Duration of Follow-up	Population, Total N	Interventions and Dosing Procedures	Inclusion / Exclusion Criteria
	• Patients assessed at week 12		reached; therefore, an additional escalation through 13.73, 17.85, 23.20, and 30.16 mg was undertaken.	• Patients with muscle invasive tumors, nodal involvement, or distant metastases; patients with a history of upper tract TCC, adenocarcinoma, or squamous cell carcinoma of the bladder; and patients with disease involving the prostatic ducts or stroma. • History of pelvic malignancy, hydronephrosis, or clinically significant abnormalities of the upper urinary tract and those who had undergone BCG therapy within 6 weeks prior to the start of VB4-845 dosing.
Pembrolizumab				

Trial Details	Design and Duration of Follow-up	Population, Total N	Interventions and Dosing Procedures	Inclusion / Exclusion Criteria
Phase II KEYNOTE 057[55,56] NCT02625961 Sponsor: Merck Estimated Completion: June 2020	Single-arm, open-label, multicenter • Patients without progression could be treated up to 24 months • Assessment of tumor status performed every 12 weeks for 2 years and then every 24 weeks for 3 years	18+ years old with high risk BCG unresponsive NMIBC with either: • Ta/T1 high-grade disease ± concomitant CIS N=96	Pembrolizumab 200 mg IV every Q3W up to 24 months	**Inclusions** • Confirmed diagnosis of high-risk non-muscle invasive TCC of the bladder (T1, high grade Ta and/or CIS) • Fully resected disease at study entry (residual CIS acceptable) • BCG-unresponsive high risk NMIBC after treatment with adequate BCG therapy • Ineligible for radical cystectomy or refusal of radical cystectomy • ECOG status of 0, 1, 2 **Exclusions** • Muscle-invasive, locally advanced nonresectable, or metastatic urothelial carcinoma • Concurrent extra-vesical non-muscle invasive transitional cell carcinoma of the urothelium • Current or past participation in study of an investigational agent and received treatment within 4 week prior to first dose • Receiving intervening intravesical chemotherapy or immunotherapy from time of most recent cystoscopy / TURBT to starting treatment • Prior therapy with anti-programmed cell death agent or agent directed to another co-inhibitory T-cell receptor
Gemcitabine				

Trial Details	Design and Duration of Follow-up	Population, Total N	Interventions and Dosing Procedures	Inclusion / Exclusion Criteria
Addeo 2010[65] Sponsor: Lega Italiana per la Lotta contro I Tumori Italy	Randomized controlled trial • Either 4 or 6 week treatment period • Toxicity measured 2 days after each infusion • Maintenance for initial responders free of recurrence monthly for first year • Follow up stopped for patients with visible tumor recurrences	TCC at stage Ta/T1 of any grade with BCG-relapse N=109	Arm 1: 4 weekly treatments of 40 mg of MMC Arm 2: 2,000 mg of gemcitabine weekly for 6 weeks In both arms, initial responders free of recurrences, maintenance therapy consisted of 10 monthly treatments for first year	**Inclusions** • Patients with a history of histologically proven recurrent TCC of the bladder at stages Ta and T1 of any grade (superficial bladder cancer whose disease has either progressed or relapsed after BCG intravesical infusion or were ineligible for BCG treatment) **Exclusions** • Prior radiation to the pelvis • Intractable urinary tract infections.
Allchorne 2014[59] Barts Healthcare National Health Service Trust in London, England	Prospective cohort study • 6-week treatment period • Response to treatment evaluated between 6 and 8 weeks after completing treatment • Cystoscopy and biopsy every 3 months	High-grade superficial (Ta/T1) bladder cancer failing BCG therapy N=19	1,500 mg gemcitabine once a week for 6 weeks	**Inclusions** • Histologically confirmed high-grade superficial (Ta/T1) bladder cancer who developed recurrent tumors despite having been treated with BCG for at least six weeks (induction course **Exclusions** • T2 disease demonstrated on CT scan • Incontinence • Patient choice
Gunelli 2007[60] Sponsor: Istituto Oncologico Romagnolo, Forlì Rome, Italy	Phase II prospective study • 6-week treatment period • Cytological analysis and cystoscopy performed at 3-month intervals for 1st year and every 6 months	18+ years old with disease recurrence (Ta G3, T1 G1-3 TCC) N=40	2,000 mg/50 ml gemcitabine on days 1 and 3 for 6 consecutive weeks (used scheme directly derived from in vitro preclinical studies included in this paper)	**Inclusions** • Patients aged 18+ with disease recurrence (Ta G3, T1 G1-3 TCC) within 6 months of one induction cycle and at least 3 maintenance cycles of BCG with no residual disease after TURB • WHO performance status 0-1 • Normal upper urinary tract and bladder capacity >300 ml were documented before recruitment with Uro-CT scan and ultrasonography

Trial Details	Design and Duration of Follow-up	Population, Total N	Interventions and Dosing Procedures	Inclusion / Exclusion Criteria
	thereafter • Lost to follow-up: n=1			**Exclusions** • **Histologically confirmed carcinoma in situ** • Previous partial cystectomy, prior pelvic irradiation and clinical evidence of other malignancies
Perdona 2010[61] Sponsor: Italian Ministry of Health - Oncology	Phase II prospective, single-arm, multicenter between 2006 and 2008 • Induction Period: 6 weeks • Treatment continues for 3 consecutive weeks at 3, 6, and 12 months • Cytological analysis of voided urine and cystoscopy were performed at 3 month intervals • Intravenous urography or compute tomography-urography performed annually • Loss to follow-up: n=0	High-risk NMIBC and refractory to BCG therapy with CIS +/- Ta, T1 tumors N=20	2,000 mg/50 ml gemcitabine twice weekly for 6 consecutive weeks (induction) and then weekly for 3 consecutive weeks at 3, 6, and 12 months	**Inclusions** • Patients with high-risk NMIBC who were refractory to BCG therapy and radical cystectomy was indicated but not performed because of patient refusal or ineligibility due to comorbidities • Received perioperative chemotherapy instillation after TUR of the bladder **Exclusions** • Concurrent or previous muscle-invasive disease, concurrent or previous tumour in the upper urinary tract or prostatic urethra, chronic urinary tract infection, cured or active tuberculosis, any other malignancy
Skinner 2013[23] NCT00234039 Sponsor: Southwest Oncology Group Collaborator: National Cancer Institute	Phase II single-arm, multicenter (16 sites) • Induction period: 6 weeks • Patients with no tumor after induction received maintenance treatment every 4 weeks for a total of 40 weeks (10	18+ years old with recurrent NMIBC stage Tis (CIS), T1, Ta high grade or multifocal Ta low grade and BCG failure N=55	2 gm intravesical gemcitabine in 100 cc saline for 1 hour once weekly for 6 weeks (induction) and then every 4 weeks for 40 weeks (maintenance, if applicable) Patients with disease	**Inclusions** • Recurrent nonmuscle invasive urothelial carcinoma after at least 2 prior courses of intravesical BCG received up to 3 years before registration • Most receipt biopsy (within 60 days of registration or 6 weeks after completion of BCG) must have shown high grade stage Ta or T1, multifocal Ta any grade or CIS +/- papillary lesions • Must have had TURBT or bladder biopsy within

Trial Details	Design and Duration of Follow-up	Population, Total N	Interventions and Dosing Procedures	Inclusion / Exclusion Criteria
	treatments) • Cystoscopy, cytology, and biopsy performed at 3 months and then cystoscopy and cytology performed every 3 months up to month 12		recurrence (appearance of new lesions of any stage or grade) were removed from protocol treatment	past 60 days documenting tumor recurrence and tumor stage and grade • Patients were allowed to have prior post-TUR chemotherapy instillations and no more than 1 induction course of other intravesical chemotherapy during year before registration • Zubrod performance status of 0 to 2 **Exclusions** • Evidence of urethral or renal pelvis TCC by upper tract radiological imaging within past 2 years
Dalbagni 2002[62] Memorial Sloan-Kettering Cancer Center Supported in part by Eli Lilly and Co.	Phase I • 3-week treatment period • 1-week break • 3-week treatment period • Serial cystoscopies every 3 months to evaluate recurrence (if recurrence - additional 2 courses could be considered)	BCG-refractory with superficial TCC (refractory CIS, multiple unresected T1 carcinoma, and uncontrollable Ta carcinoma) N=18	500 mg gemcitabine 1,000 mg gemcitabine 1,500 mg gemcitabine 2,000 mg gemcitabine Twice weekly for 3 consecutive weeks, 1week break, and then 3 more consecutive weeks	**Inclusions** • Superficial TCC refractory to BCG therapy where a cystectomy was recommended but refused • Stages of disease included refractory CIS, multiple unresected T1 carcinoma, and uncontrollable Ta carcinoma • Karnofsky performance status greater than 70% **Exclusions** • Prior radiation to the pelvis and intractable urinary tract infection
Dalbagni 2006[22] Memorial Sloan-Kettering Cancer Center Supported by Eli Lilly and Co.	Phase II • 3-week treatment period • 1-week break • 3-week treatment period • Evaluated for response at 8 weeks and then every 3 months to 1 year.	BCG-refractory or intolerant with superficial TCC (refractory CIS, multiple unresected T1 carcinoma, and uncontrollable Ta carcinoma) N=30	2,000 mg/100 mL twice weekly for 3 consecutive weeks, each course separated by 1 week of rest	**Inclusions** • Superficial TCC refractory or intolerant to BCG therapy where a cystectomy was recommended but refused • Stages of disease included refractory CIS, multiple unresected T1 carcinoma, and uncontrollable Ta carcinoma • Karnofsky performance status greater than 70% **Exclusions**

Trial Details	Design and Duration of Follow-up	Population, Total N	Interventions and Dosing Procedures	Inclusion / Exclusion Criteria
				• Prior radiation to the pelvis and intractable urinary tract infection
Di Lorenzo 2010[66] Naples, Italy	Phase II prospective, multicenter, randomized study between 2006 and 2008 in Italy • Treatment weekly for 6 week and then weekly for 3 consecutive weeks at 3, 6, and 12 months • Cytological urine analysis and cystoscopy every 3 months, intravenous or CT-scan urography every 12 months • Loss to follow-up: n=0	High-risk NMIBC failing 1 course of BCG therapy N=80	Cohort 1: 2,000 mg/50 mL gemcitabine twice weekly for 6 weeks then weekly for 3 consecutive weeks at 3, 6, and 12 months (n=40) Cohort 2: 81mg/50mL BCG weekly for 6 week then 3 weekly instillations at 3, 6, 8 and 12 months (n=40)	**Inclusions** • High-risk NMIBC, failing BCG therapy, for whom radical cystectomy was indicated but not done based on refusal or ineligibility (age, comorbidities, high anesthesiological risk) **Exclusions** • Concurrent or previous muscle-invasive disease, concurrent or previous tumour in the upper urinary tract or prostatic urethra, cured or active tuberculosis, any other malignancy
Bartoletti 2005[117] Department of Urology, University of Florence Department of	Non-randomized, prospective, Phase II Multicenter: 5 urology departments in Tuscany, Italy • 6 month enrollment period	35 years or older with histologically confirmed stage Ta, T1 or CIS TCC of the bladder N=116	2000 mg gemcitabine once a week for 6 weeks (one cycle)	**Inclusions** • Presence of superficial TCC classified as intermediate-risk or high-risk • ECOG performance status of 0 or 1 • No urinary infection • Normal preoperative blood tests and ability to follow instillation and follow up schedules • Could have received prior intravesical treatment

Trial Details	Design and Duration of Follow-up	Population, Total N	Interventions and Dosing Procedures	Inclusion / Exclusion Criteria
Urology, University of Florence	• 6 week treatment period • Follow up tests one month after last instillation • In tumor free cases, cystoscopy and urinary cytology were repeated at 3 month intervals for first 2 years, 6 month intervals for the next 3 years and annually thereafter. Ultrasonography of the urinary tract required every 6 months • Loss to follow-up: n=2			(had to have been more than 6 months before transurethral resection) **Exclusions** • Evidence of locally infiltrative or metastatic bladder tumors (stage T2 or greater), presence of upper urinary tract tumors, lesions that could not be completely removed transurethrally • Aged 35 years or younger or older than 85 • Lower urinary tract disease
Fiorito 2014[64] Italy	Long-term results of a Phase II study on second line intravesical gemcitabine - abstract • 6-week treatment period • Overall survival, cancer specific survival, disease free survival, and progression free survival assessed at last follow-up Median follow-up: 72 (22-96) months for all patients	Intermediate-risk NMIBC recurring after BCG patients N=41	2 mg gemcitabine weekly for 6 weeks	**Inclusions** • Patients with intermediate risk NMIBC recurring after at least a complete induction of BCG **Exclusions** • NR
Sternberg 2013[67]	Retrospective chart review between Jan 1999	Patients with NMIBC tumors with BCG failure	Two courses of 2000 mg gemcitabine twice	**Inclusions**

Trial Details	Design and Duration of Follow-up	Population, Total N	Interventions and Dosing Procedures	Inclusion / Exclusion Criteria
	and Oct 2011 • 3-week treatment period separated by weeks of rest for a total of 12 instillations	N=69	weekly for 3 weeks with courses separated by a week of rest for a total of 12 instillations	• Patients with NMIBC tumors who were treated with intravesical gemcitabine after failure of BCG treatment **Exclusions** • NR
Gemcitabine with Docetaxel				

Trial Details	Design and Duration of Follow-up	Population, Total N	Interventions and Dosing Procedures	Inclusion / Exclusion Criteria
Steinberg 2020[118] Supported by John & Carol Walter Family Foundation	US multicenter retrospective study reviewing patients records between June 2009 and May 2018 • Surveillance initiated 12 to 16 weeks from beginning of GEM/DOC induction • If patients were found to be initial responders (disease free at 4 months) some went on to received maintenance instillations • All institutions used monthly maintenance schedule for 24 months except 2 institutions that used SWOG schedule • Surveillance cystoscopy every 3 month for 2 years and every 6 months if disease free beyond 2 years • Loss to follow-up: n=2	Patients with recurrent NMIBC and a history of BCG treatment N=276	1 gm gemcitabine in 50 ml sterile water or normal saline instilled for either 60 or 90 minutes (depending on institutional protocol) and 37.5 mg docetaxel in 50 ml saline Induction regimen administered weekly for 6 weeks	**Inclusions** • Patients with recurrent NMIBC and a history of prior BCG treatment **Exclusions** • Patients with no surveillance follow-up or if alternative regimens that use the study agents were adopted (e.g. Gem/Doce induction and BCG maintenance)

Trial Details	Design and Duration of Follow-up	Population, Total N	Interventions and Dosing Procedures	Inclusion / Exclusion Criteria
Daniels 2020[70]	Retrospective study from patients from 2 US academic institutions between years 2013 and 2018 • If eligible for maintenance, GEM/DOCE given monthly with cystoscopies performed every 3 months • At follow-up, blood and urine tests, urine cytology, and cystoscopy were evaluated	Patients who received full gemcitabine/docetaxel for NMIBC between 2013 and 2018 N=59	1 gm gemcitabine in 76.32 ml of normal saline solution for 60 minutes and 40 mg of docetaxel in 54 ml of normal saline solution 6 weekly instillations of gemcitabine/docetaxel and subsequent monthly maintenance instillations for those with no evidence of disease at first surveillance	**Inclusions** • Received sequential gemcitabine and docetaxel for biopsy-proven NMIBC between 2013 and 2018 from the IRB approved registries of 2 academic institutions **Exclusions** • NR
Steinberg 2015[72] University of Iowa	Retrospective study reviewing patients at the University of Iowa Hospitals and Clinics between June 2009 and May 2014 • Surveillance initiated 12 to 16 weeks from beginning of GEM/DOC induction • Patients found to be recurrence free received monthly maintenance instillations for 24 months • Surveillance cystoscopy every 3 month for 2 years and every 6 months	Patients treated with sequential intravesical gemcitabine/docetaxel for NMIBC between 2009 and 2014 N=45	1 gm gemcitabine in 50 ml sterile water or normal saline instilled for 90 minutes and 37.5 mg docetaxel in 50 ml saline Induction regimen administered weekly for 6 weeks	**Inclusions** • Received sequential gemcitabine and docetaxel for NMIBC between 2009 and 2014 **Exclusions** • NR

Trial Details	Design and Duration of Follow-up	Population, Total N	Interventions and Dosing Procedures	Inclusion / Exclusion Criteria
	if disease free beyond 2 years			
Milbar 2017[71]	Retrospective study reviewing patients from the Johns Hopkins Non-Muscle Invasive Bladder Cancer database between 2003 and 2016 • Recurrence evaluated within 6 months of gemcitabine/docetaxel induction	Patients receiving sequential gemcitabine/docetaxel from 2003 to 2016 N=33	1 gm gemcitabine in 50 ml sterile water instilled into bladder for 60 minutes. Then bladder is drained and 37.5 mg docetaxel in 50 ml normal saline for 60 minutes. Induction regimen administered weekly for 6 weeks	**Inclusions** • Received sequential GEM/DOC for NMIBC between 2009 and 2014 **Exclusions** • NR

Trial Details	Design and Duration of Follow-up	Population, Total N	Interventions and Dosing Procedures	Inclusion / Exclusion Criteria
Caruso 2020[17]	Prospective Study • Treatment for 6 weeks • Cystoscopy and full bladder mapping and cytology at 12 weeks • Cystoscopy every 3 months for one year and 3 months or 6 months thereafter	Patients who had failed or were intolerant to BCG therapy N=26	1000 mg of GEM in 100 cc's saline followed by 37,5 mg DOC in 50 mls saline weekly for 6 weeks.	**Inclusion Criteria:** • Patients who had failed or were intolerant to BCG therapy **Exclusion Criteria:** • NR

BC: bladder cancer, BCG: bacillus calmette guerin, CIS: carcinoma in situ, CT: computerized tomography, ECOG: eastern cooperative oncology group, EpCAM: epithelial cell adhesion molecule, GEM/DOC: gemcitabine/docetaxel, mg/mL: milligram per milliliter, n: number, N: total number, NMIBC: non muscle invasive bladder cancer, Q3W: every 3 weeks, rAd-IFN/Syn3: recombinant adenovirus delivered inferferon alpha 2-b with Syn3, SWOG: National Cancer Institute supported Organization, Ta: non-invasive papillary tumor, T1: tumor invading subepithelial connective tissue, TCC: transitional cell carcinoma, Tis: in situ carcinoma, TUR: trans urethral resection, TURBT: trans urethral resection of bladder tumor

Table D2. Baseline Characteristics

Trial	Arms	N	Age, Years Median (IQR)	Race, n (%)				Sex, n (%)		Prior BCG Classification		Number of Previous BCG Courses, n (%)		Primary Tumor Classification at Enrollment, n (%)	
				White	Black	Asian	Other	Female	Male	Relapsed	Refractory	1	≥ 2	CIS ±T1/Ta	High grade Ta/T1 alone
Nadofaragene Firadenovec															
Phase III[19]	CIS ± T1/Ta	107	72 (66-77)	99 (92.5)	6 (5.6)	2 (1.9)	0 (0)	12 (11.2)	95 (88.8)	NR	NR	1 (0.9)	106 (99.1)	107 (100)	0 (0)
	High-grade Ta/T1	50	71 (64-78)	47 (94.0)	2 (4.0)	1 (2.0)	0 (0)	16 (32)	34 (68.0)	NR	NR	5 (10.0)	45 (90.0)	0 (0)	50 (100)
	Overall	157	71 (66-77)	146 (93.0)	8 (5.1)	3 (1.9)	0 (0)	28 (17.8)	129 (82.2)	NR	NR	6 (3.8)	151 (96.2)	107 (68.1)	50 (31.8)

Trial	Arms	N	Age, Years Median (IQR)	Race, n (%)				Sex, n (%)		Prior BCG Classification		Number of Previous BCG Courses, n (%)		Primary Tumor Classification at Enrollment, n (%)	
				White	Black	Asian	Other	Female	Male	Relapsed	Refractory	1	≥ 2	CIS ±T1/Ta	High grade Ta/T1 alone
Phase II SUO-CTC[50]	rAd-IFN 1x10^{11} vps/mL (low-dose)	21	70 (67-74)	NR	NR	NR	NR	2 (9.5)	19 (90)	10 (47.6)	11 (52.4)	1 (4.8)	20 (95.2)	17 (81)	4 (19)
	rAd-IFN 3x10^{11} vps/mL (high-dose)	19	73 (62-81)	NR	NR	NR	NR	5 (26.3)	14 (73.7)	9 (47.4)	10 (52.6)	1 (5.3)	18 (94.7)	13 (68.2)	6 (31.9)
Phase I Dinner 2013[51]	rAd-IFN 3x10^{9} to 3x10^{11} vps/mL	17	No overall presented - only individual patient-level data												
Oportuzumab Monatox															
Phase III VISTA[20,52]	Overall	133	Mean, SD: 73.5 (8.79)	124 (93)	5 (4)	3 (2)	1 (<1)	30 (23)	103 (77)	NR	NR	Mean: 3 Median: 3 Range: 2-13		93 (70)	40 (30)
Phase II Kowalski 2012[53]	Cohort 1: Vicineum 30mg	22	Median (range): 75 (41-89)	21 (95.5)	0 (0)	NR	1 (4.5)	6 (27.3)	16 (72.7)	0 (0)	22 (100)	Mean: 2.15 (± 1.7) Range: 1 - 8		22 (100)	0 (0)
	Cohort 2: Vicineum 30mg	23	Median (range): 72 (54-92)	22 (95.7)	1 (4.3)	NR	0 (0)	4 (17.4)	19 (82.6)	2 (9)	21 (91)			23 (100)	0 (0)
Phase I Kowalski 2010[54]	Overall	64	69 (NR)	64 (100)	0 (0)	0 (0)	0 (0)	14 (22)	50 (78)	0 (0)	62 (97)	27 (42)	35 (55)	17 (27)	47 (73)
Pembrolizumab															
Phase II KEYNOTE 057[55,56]	Pembrolizumab 200 mg	96	73 (44-92)	64 (66.7)	0 (0)	26 (27.1)	6 (6.3)	15 (15.6)	81 (84.4)	NR	NR	Median instillations, n (range): 12 (7-45)		96 (100)	0 (0)
Gemcitabine															
Addeo 2010[65]	Gemcitabine	54	Mean, SD: 64.9 (10.5)	NR	NR	NR	NR	8 (15)	46 (85)	NR	NR	Previous BCG: 46/54		0 (0)	54 (100)
	Mitomycin	55	Mean, SD: 67.9 (10.2)	NR	NR	NR	NR	8 (15)	47 (85)	NR	NR	Previous BCG: 45/55		0 (0)	55 (100)
Allchorne 2014[59]	Gemcitabine	19	Mean, SD: 69.79 (12.85)	NR	NR	NR	NR	7 (36.8)	12 (63.2)	0 (0)	19 (100)	11 (58)	8 (42)	0 (0)	19 (100)
Gunelli 2007[60]	Gemcitabine	40	<60: 10 (25), 60-74: 17 (42.5), ≥ 75: 13 (32.5)	NR	NR	NR	NR	2 (5)	38 (92.5)	0 (0)	40 (100)	NR	NR	N/A	40 (0)
Perdona 2010[61]	Gemcitabine	20	Mean (SD): 68.3 (5.4)	NR	NR	NR	NR	7 (35)	13 (65)	0 (0)	20 (100)	NR	NR	7 (35)	13 (65)
Skinner 2013[23]	Gemcitabine	47	70 (50-88)	43 (91)	0 (0)	3 (6)	1 (2)	14 (30)	33 (70)	37 (79)	9 (19)	15 (32)	26 (55)	28 (6)	19 (40)
Dalbagni 2002[62]	Gemcitabine	18	74 (37-86)	NR	NR	NR	NR	4 (22)	14 (78)	NR	NR	3 (16.6)	10 (55.5)	14 (77.8)	4 (22.2)

Trial	Arms	N	Age, Years Median (IQR)	Race, n (%)				Sex, n (%)		Prior BCG Classification		Number of Previous BCG Courses, n (%)		Primary Tumor Classification at Enrollment, n (%)	
				White	Black	Asian	Other	Female	Male	Relapsed	Refractory	1	≥ 2	CIS ±T1/Ta	High grade Ta/T1 alone
Dalbagni 2006[22]	Gemcitabine	30	70 (43-89)	NR	NR	NR	NR	8 (26.6)	22 (73.3)	0 (0)	30 (100)	9 (30)	13 (43.3)	28 (93.3)	2 (6.6)
Di Lorenzo 2010[66]	Cohort 1: Gemcitabine	40	Mean (SD): 69.3 (8.4)	NR	NR	NR	NR	13 (32.5)	27 (67.5)	NR	NR	NR	NR	12 (30)	28 (70)
	Cohort 2: BCG	40	Mean (SD): 71.4 (7.9)	NR	NR	NR	NR	18 (45)	22 (55)	NR	NR	NR	NR	13 (32)	27 (68)
Bartoletti 2005[117]	Gemcitabine - Overall Population	116	Mean (SD): 68 (9)	NR	NR	NR	NR	15 (12.9)	101 (87.1)	NR	40 (34)	NR	NR	11 (9)	105 (91)
Fiorito 2014[64]	Gemcitabine	41	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Sternberg 2013[67]	BCG Refractory	37	71 (63-75)	NR	NR	NR	NR	10 (27)	27 (73)	0 (0)	37 (100)	NR	NR	29 (78)	8 (22)
	Other BCG Failures	32	73 (63-77)	NR	NR	NR	NR	6 (19)	26 (81)	NR	NR	NR	NR	18 (60)	12 (40)
Gemcitabine/Docetaxel															
Steinberg 2020[118]	Gemcitabine/ Docetaxel	276	73 (43-94)	241 (87.3)	4 (1.5)	3 (1.1)	8 (3)	52 (18.8)	224 (81.2)	102 (37.0)	127 (46.0)	146 (52.9)	128 (46.4)	173 (62.7)	72 (26.1)
Daniels 2020[70]	Gemcitabine/ Docetaxel	59	Mean (SD): 72.4 (10.4)	49 (83.1)	5 (8.5)	2 (3.4)	3 (5)	9 (15.3	50 (84.7)	NR	31 (63)	NR	NR	24 (41)	35 (59)
Steinberg 2015[72]	Gemcitabine/ Docetaxel	45	72 (50-91)	42 (93)	NR	NR	3 (7)	8 (18)	37 (82)	18 (40)	23 (51)	Median (range): 2 (0-4)		29 (64)	16 (36)
Milbar 2017[71]	BCG-Unresponsive/ Relapsing Cohort	25	72.9 (10.8)	21 (84)	NR	NR	4 (16)	5 (20)	20 (80)	NR	22 (66)	NR	NR	14 (56)	8 (32)
Caruso 2020[17]	Gemcitabine/ Docetaxel	26	77 (68-94)	NR	NR	NR	NR	6 (23)	20 (77)	NR	NR	Mean: 3.2 of prior intravesical therapy		NR	NR

BCG: bacillus calmette guerin, CIS: carcinoma in situ, IQR: interquartile range, mg: milligram, n: number, N: total number, NR: not reported, rAd-IFN/Syn3: recombinant adenovirus delivered inferferon alpha 2-b with Syn3, SD: standard deviation, Ta: non-invasive papillary tumor, T1: tumor invading subepithelial connective tissue

Table D3. Efficacy Outcomes

Trial	Arms / Population	N	*Complete Response, n (%)*				*High Grade Recurrence Free Survival , n (%)*					Median Time to Recurrence, months	Disease Recurrence, n (%)	Disease Progression, n (%)	Progression to ≥ MIBC
			months				*months*								
			3	6	9	12	3	6	9	12	24				
Nadofaragene Firadenovec															
Phase III[19,25]	CIS ± Ta/T1 disease	103	55 (53.4)	NA	NA	NA	55 (53.4)	42 (40.8)	36 (35.0)	25 (24.3)	NR	NR	NR	5 (4.9)	
	Ta/T1 papillary disease	48	35 (72.9)	NA	NA	NA	35 (72.9)	30 (62.5)	28 (58.3)	21 (43.8)	NR	NR	NR	3 (6.3)	
	Overall	151	90 (59.6)	NA	NA	NA	90 (59.6)	72 (47.7)	64 (42.4)	46 (30.5)	NR	NR	NR	8 (5)	
Phase II SUO-CTC[50]	rAd-IFN $1x10^{11}$ vps/mL (low-dose)	21	NR	NR	NR	NR	10 (47.6)	8 (38.1)	8 (38.1)	7 (33.3)	NR	3.52	NR	NR	NR
	rAd-IFN $3x10^{11}$ vps/mL (high-dose)	19	NR	NR	NR	NR	13 (68.4)	9 (47.4)	9 (47.4)	7 (36.8)	NR	11.73	NR	NR	NR
	Overall	40	NR	NR	NR	NR	23 (57.5)	17 (42.5)	17 (42.5)	14 (35.0)	NR	NR	26 (65)	NR	NR
Phase I Dinney 2013 [51]	Overall: $3x10^{9}$ to $3x10^{11}$ vps/mL	17	7 (41)	2 remained disease free at 29 and 39.2 months respectively			NR	NR	NR	NR	NR	NR	8/14 on dose levels 2-5		NR
	rAd-IFN doses ≥ $1x10^{11}$ vps/mL	13	6 (43)	NR	NR	5 (36)	NR	NR	NR	NR	NR	Mean: 31	NR	NR	NR
Oportuzumab Monatox															
Phase III VISTA[20,52]	CIS ± Ta/T1 disease	89	36 (40)	25 (28)	19 (21)	15 (17)	NA	NA	NA	NA	NA	287 Days (9.4 months)	NR	NR	NR
	Ta/T1 Papillary disease	38	NA	NA	NA	NA	27 (71.0)	22 (58.0)	17 (45.0)	16 (42.0)	NA	402 Days (13.2 months)	NR	NR	NR

Trial	Arms / Population	N	*Complete Response, n (%)*				*High Grade Recurrence Free Survival , n (%)*					Median Time to Recurrence, months	Disease Recurrence, n (%)	Disease Progression, n (%)	Progression to ≥ MIBC
			months				*months*								
			3	6	9	12	3	6	9	12	24				
	Overall	127	NA	NA	NA	NA	NR	NR	NR	NR	NR	NR	NR	NR	NR
Phase II Kowalski 2012[53]	Cohort 1: Vicineum 30 mg	22	9 (40.9)	6 (27.3)	3 (13.6)	3 (13.6)	NR	NR	NR	NR	NR	274 Days	8 (73), n=11	1 (5)	NR
	Cohort 2: Vicineum 30 mg	23	9 (39.1)	6 (26.1)	5 (21.7)	4 (17.4)	NR	NR	NR	NR	NR	408 Days	5 (55.5), n=9	1 (4)	NR
Phase I Kowalski 2010[54]	Overall	61	4-6 weeks following last dose: 24 (39) Significant difference between lowest dose groups and combine middle and high (p=0.0418)				NR	NR	NR	NR	NR	NR	NR	NR	NR
Pembrolizumab															
Phase II KEYNOTE 057[55,56]	Overall: CIS ± Ta/T1 disease	96	39 (40.6)	36 (38)	27 (28)	18 (19)	NR	NR	NR	NR	NR	16.2 (0-30.4)	20 (47.6)	NR	0 (0)
Gemcitabine															
Addeo 2010[65]	Gemcitabine	54	NR	NR	NR	NR	NR	NR (97)*	NR (83)*	NR (72)*	NR (50)*	Not Reached	Relative Risk: 0.72	6 (11)	NR
	Mitomycin	55	NR	NR	NR	NR	NR	NR (93)*	NR (73)*	NR (56)*	NR (39)*	15	Relative Risk: 0.94	10 (18)	NR
Allchorne 2014[59]	Gemcitabine	19	NR	NR	NR	NR	NR	NR	NR	8 (42)	NR	8 (2-62)	12 (63)	NR	NR
Gunelli 2007[60]	Gemcitabine	40	NR	38 (95)	NR	NR	NR	37 (95)*	NR	30 (82)*	14 (66)*	NR	14 (35)	NR	NR
Perdona 2010[61]	Gemcitabine	20	15 (75)	NR	NR	NR	NR (89)*	NR (67)*	NR (60)*	NR (50)	NR (38)	3.5	11 (55)	5 (45)	5 (45)
Skinner 2013[23]	Gemcitabine	47	19 (40)	NR	NR	NR	NR (54)*	NR (53)*	NR (30)*	13 (28)*	10 (21)*	6.1	40 (85)	17 (36)	NR

Trial	Arms / Population	N	*Complete Response, n (%)*				*High Grade Recurrence Free Survival , n (%)*					Median Time to Recurrence, months	Disease Recurrence, n (%)	Disease Progression, n (%)	Progression to ≥ MIBC
			months				*months*								
			3	6	9	12	3	6	9	12	24				
Dalbagni 2002[62]	Gemcitabine	18	Time point at 8 weeks: 7 (39)				NR	NR	NR	NR	NR	NR	NR	NR	NR
Dalbagni 2006[22]	Gemcitabine	30	15 (50)	NR	NR	NR	NR (93)*	NR (28)*	NR (27)*	3 (21)	NR (15)*	3.6	12 (86)	1 (0.7)	NR
Di Lorenzo 2010[66]	Cohort 1: Gemcitabine	40	NR	NR	NR	NR	NR (97)*	NR (80)*	NR (70)*	NR (53)*	NR (19)	3.9	21 (52.5)	7 (33)	NR
	Cohort 2: BCG	40	NR	NR	NR	NR	NR (86)*	NR (62)*	NR (41)*	NR (26)*	NR (3)	3.1	35 (87.5)	13 (37.5)	NR
Bartoletti 2005[117]	Gemcitabine	40	NR	NR	NR	NR	NR	NR	NR	27 (68)	NR	NR	13 (32.5)	NR	NR
Fiorito 2014[64]	Gemcitabine	41	NR	NR	NR	19/39 (48.7)	NR	NR	NR	NR	NR	7.5 (3-73)	19 (48.7)	NR	1 (2.6)
Sternberg 2013[67]	Gemcitabine	69	27 (39)	NR	NR	NR	NR	NR	NR	NR	NR	NR	46 (67)	11 (16)	NR
Gemcitabine/Docetaxel															
Steinberg 2020[118]	Gem/Doc	276	NR	NR	NR	NR	NR	NR	(~79%)	179 (65)	144 (52)	6.8	NR	21 (7.6)	11 (4)
Daniels 2020[70]	Gem/Doc	59	37 (71)	NR	NR	NR	NR	NR	NR	28 (53)	18 (35)	NR	16 (27)	NR	NR
Steinberg 2015[72]	Gem/Doc	45	NR	NR	NR	NR	30 (66)	NR	NR	24 (54)	15 (34)	5.9	NR	NR	NR
Milbar 2017[71]	BCG-Unresponsive/Relapsing Cohort	25	NR	NR	NR	NR	NR	NR	NR	12 (49)	9 (34)	6.5	15 (60)	NR	NR
Caruso 2020[17]	Gem/Doc	26	24 (92)	NR	NR	NR	NR	NR	NR	NR	NR	Mean disease free interval: 12.45 months, (Range 3-34)	16 (62)	3 (12)	7 (7.7)

CIS: carcinoma in situ, Gem/Doc: gemcitabine/docetaxel, MIBC: muscle invasive bladder cancer, n: number, N: total, NR: not reported, rAd-IFN/Syn3: recombinant adenovirus delivered inferferon alpha 2-b with Syn3, SD: standard deviation, Ta: non-invasive papillary tumor, T1: tumor invading subepithelial connective tissue
*Digitized estimates

Table D4. Efficacy Subgroups

	Time Point: Months	3	6	9	12	24	Duration of Response, median (95%CI)
Nadofaragene Firadenovec							
Phase III[19,24,25]	***Complete Response Rate, n (%; 95%CI)***						
	CIS ± Ta/T1 (n= 107)	55 (53.4; 43.3-63.3)	NA	NA	NA	NA	9.69 (9.17-NE)
	High-grade Ta/T1 alone (n= 50)	35 (72.9; 58.2-84.7)	NA	NA	NA	NA	NA
	1+ Prior BCG Cycles	NR	NR	NR	NR	NR	NR
	2+ Prior BCG Cycles	NR	NR	NR	NR	NR	NR
	High-Grade Recurrence Free Survival, n (%)						
	Overall (n= 157)	90 (59.6; 51.3-67.5)	72 (47.7; 39.5-56.0)	64 (42.4; 34.4-50.7)	46 (30.5; 23.2-38.5)	NR	7.31 (5.68-11.93)*
	CIS ± Ta/T1 (n= 107)	55 (53.4; 43.3-63.3)	42 (40.8; 31.2-50.9)	36 (35.0; 25.8-45.0)	25 (24.3; 16.4-33.7)	NR	NA
	High-grade Ta/T1 alone (n= 50)	35 (72.9; 58.2-84.7)	30 (62.5; 47.4-76.0)	28 (58.3; 43.2-72.4)	21 (43.8; 29.5-58.8)	NR	12.35 (6.67-NE)
	1+ Prior BCG Cycles	NR	NR	NR	NR	NR	NR
	2+ Prior BCG Cycles	NR	NR	NR	NR	NR	NR
	Progression						
	Overall (n= 157)	NR	NR	NR	8 (5)	NR	NA
	CIS ± Ta/T1 (n= 107)	NR	NR	NR	5 (4.9)	NR	NA
	High-grade Ta/T1 alone (n= 50)	NR	NR	NR	3 (6.3)	NR	NA
	1+ Prior BCG Cycles	NR	NR	NR	NR	NR	NA
	2+ Prior BCG Cycles	NR	NR	NR	NR	NR	NA
	Cystectomy						
	Overall (n= 157)	NR	NR	NR	40 (26)	NR	NA

	Time Point: Months	3	6	9	12	24	Duration of Response, median (95%CI)
	CIS ± Ta/T1 (n= 107)	NR	NR	NR	30 (29)	NR	Median time to Cystectomy: 8.87 months (IQR 4.93 – 11.01)
	High-grade Ta/T1 alone (n= 50)	NR	NR	NR	10 (21)	NR	Median time to Cystectomy: 8.31 months (IQR: 5.78 – 13.11)
	1+ Prior BCG Cycles	NR	NR	NR	NR	NR	NA
	2+ Prior BCG Cycles	NR	NR	NR	NR	NR	NA
Oportuzumab Monatox							
Phase III[20]	***Complete Response Rate, n (%; 95% CI)***						
	Overall (n=127)	NA	NA	NA	NA	NA	NA
	CIS ± Ta/T1 (n=89)	36 (40; 30-51)	25 (28; 19-39)	19 (21; 13-31)	15 (17; 10-26)	NR	287.0 days (154.0 - N/E; range: 89-651 days)
	High-grade Ta/T1 alone (n=38)	NR	NR	NR	NR	NR	NR
	2 Prior BCG Cycles (n=42)	16 (38; 24-54)	14 (33; 20-50)	12 (29; 16-45)	9 (21; 10-37)	NR	Not reached (273.0 days - N/E; range 106-644 days)
	≥3 Prior BCG Cycles (n=47)	20 (43; 28-58)	11 (23; 12-38)	7 (15; 6-28)	6 (13; 5-26)	NR	160.5 days (96.0 days - 290.0 days; range: 89-651 days)
	High-Grade Recurrence Free Survival, n (%)						
	Overall (n=127)	NR	NR	NR	NR	NR	NR
	CIS ± Ta/T1 (n=89)	NA	NA	NA	NA	NA	NR
	High-grade Ta/T1 alone (n=38)	27 (71.0)	22 (58.0)	17 (45.0)	16 (42.0)	NA	NR
	2 Prior BCG Cycles (n=65), n (95% CI)	51 (38-63)	44 (32-57)	37 (25-49)	31 (19-43)	27 (16-39)	NR
	≥3 Prior BCG Cycles (n=68), n (95% CI)	49 (37-61)	35 (24-47)	26 (16-37)	26 (16-37)	15 (6-24)	NR
	Progression						
	Overall	100 (NA)	99 (97-N/E)	96 (90-N/E)	96 (90-N/E)	90 (76-N/E)	NR
	CIS ± Ta/T1	100 (NA)	98 (95-N/E)	94 (84-N/E)	94 (84-N/E)	94 (84-N/E)	NR

	Time Point: Months	3	6	9	12	24	Duration of Response, median (95%CI)
	High-grade Ta/T1 alone	100 (NA)	100 (NA)	100 (NA)	100 (NA)	88 (65-N/E)	NR
	2 Prior BCG Cycles	100 (NA)	100 (NA)	100 (NA)	100 (NA)	100 (NA)	NR
	≥3 Prior BCG Cycles	100 (NA)	98 (94-N/E)	92 (81-N/E)	92 (81-N/E)	81 (57-N/E)	NR
	Cystectomy-Free Survival (Kaplan-Meier Estimate), % (95% CI)						
	Overall (n=133)	99 (98-N/E)	94 (90-98)	88 (83-94)	84 (77-90)	76 (67-85)	NR
	CIS ± Ta/T1 (n=93)	99 (97-N/E)	94 (89-99)	87 (80-94)	81 (73-90)	71 (59-83)	NR
	High-grade Ta/T1 alone (n=40)	100	94 (87-N/E)	92 (83-N/E)	89 (78-99)	85 (72-97)	NR
	2 Prior BCG Cycles(n=65)	100	93 (87-100)	86 (77-95)	82 (72-92)	76 (63-88)	NR
	≥3 Prior BCG Cycles (n=68)	99 (96-N/E)	95 (90-N/E)	90 (83-98)	85 (76-94)	76 (63-89)	NR
Pembrolizumab							
Phase II KEYNOTE 057[21,55,56]	***Complete Response Rate, n (%), 95% CI***						
	Overall (n= 96)	NA	NA	NA	NA	NA	NA
	CIS ± Ta/T1	39 (41), 31-51	NR	NR	NR (19)	NA	NA
	High-grade Ta/T1 alone	NA	NA	NA	NA	NA	NA
	1+ Prior BCG Cycles	NA	NA	NA	NA	NA	NA
	2+ Prior BCG Cycles	NA	NA	NA	NA	NA	NA
	High-Grade Recurrence Free Survival						
	Overall (n= 96)	NA	NA	NA	NA	NA	NA
	CIS ± Ta/T1	NR (40.6)	NR (37.5)	NR (28.1)	NR (18.8)	NR	16.2 months (Range 0-30.4)
	High-grade Ta/T1 alone	NA	NA	NA	NA	NA	NA
	1+ Prior BCG Cycles	NA	NA	NA	NA	NA	NA
	2+ Prior BCG Cycles	NA	NA	NA	NA	NA	NA
	Progression						
	Overall (n= 96)	NA	NA	NA	NA	NA	NA

	Time Point: Months	3	6	9	12	24	Duration of Response, median (95%CI)
	CIS ± Ta/T1	NA	NA	NA	NA	NA	NA
	High-grade Ta/T1 alone	NA	NA	NA	NA	NA	NA
	1+ Prior BCG Cycles	NA	NA	NA	NA	NA	NA
	2+ Prior BCG Cycles	NA	NA	NA	NA	NA	NA
	Cystectomy						
	Overall (n= 96)	NA	NA	NA	NA	NA	NA
	CIS ± Ta/T1	NA	NA	NA	NA	NA	NA
	High-grade Ta/T1 alone	NA	NA	NA	NA	NA	NA
	1+ Prior BCG Cycles	NA	NA	NA	NA	NA	NA
	2+ Prior BCG Cycles	NA	NA	NA	NA	NA	NA

95% CI: 95% confidence interval, BCG: bacillus calmette guerin, CIS: carcinoma in situ, n: number, N: total, NA: not applicable, N/E: not eligible, NR: not reported, rAd-IFN/Syn3: recombinant adenovirus delivered inferferon alpha 2-b with Syn3, SD: standard deviation, Ta: non-invasive papillary tumor, T1: tumor invading subepithelial connective tissue

* Median duration of response for the overall population includes a mixture of CR for CIS ± Ta/T1 and HGRFS for the Ta/T1 population.

Table D5. Safety I

Trial	Arms	N	Any AE	Any SAE	Treatment-related AE	Any Grade 3-5 AEs	Treatment-related AE Grade 3-5	Treatment-related SAEs	Discontinuation due to any AEs	Death
			n (%)							
Nadofaragene Firadenovec										
Phase III[19]	rAd-IFN	157	146 (93)*	14 (9)*	110 (70)	29 (19)*	6 (4)	3 (2)	3 (1.9)*	6 (3.8) †
Phase II SUO-CTC[50]	rAd-IFN 1x10^{11} vps/mL (low-dose)	21	20 (95)	3 (14.3)	18 (87.5)	NR	NR	NR	0 (0)	NR
	rAd-IFN 3x10^{11} vps/mL (high-dose)	19	19 (100)	2 (10.5)	16 (84.2)	NR	NR	NR	0 (0)	NR
	Overall	40	39 (97.5)	5 (12.8)	34 (85)	NR	9 (22)	NR	0 (0)	7 (18)
Phase I Dinney 2013[51]	Overall	17	17 (100)	1 (6)	NR	NR	NR	NR	0 (0)	3 (18)
Oportuzumab Monatox										
Phase III VISTA[20,52]	Overall	132	117 (88)*	19 (14)*	66 (50)	29 (22)*	5 (4)	3 (2)	4 (3)*	1 (<1)
Phase II Kowalski 2012[53]	Overall	45	43 (94)	6 (13)	30 (65)	9 (20)	3 (7)	0 (0)	0 (0)	0 (0)
Phase I Kowalski 2010[54]	Overall	64	41 (64)	0 (0)	20 (31)	0 (0)	1 (2)	0 (0)	0 (0)	1 (2)
Pembrolizumab										
Phase II KEYNOTE 057[55,56]	Pembrolizumab 200 mg	96	99 (97.1)	26 (25.5)	67 (65.7)	30 (29.4)	13 (12.7)	8 (7.8)	10 (9.8)	2 (2)
Gemcitabine										
Addeo 2010[65]	Gemcitabine	54	21 (38.8)	NR	NR	NR	NR	NR	NR	NR
	Mitomycin	55	40 (72.2)	NR	NR	NR	NR	NR	NR	NR
Allchorne 2014[59]	Gemcitabine	19	NR	NR	NR	NR	NR	NR	NR	NR
Gunelli 2007[60]	Gemcitabine	40	NR	NR	NR	NR	NR	NR	NR	NR
Perdona 2010[61]	Gemcitabine	20	NR	NR	NR	NR	NR	NR	NR	NR
Skinner 2013[23]	Gemcitabine	55	37 (67)	NR	NR	3 (5)	NR	NR	NR	8 (17)
Dalbagni 2002[62]	Gemcitabine	18	NR	NR	NR	NR	NR	NR	NR	NR
Dalbagni 2006[22]	Gemcitabine	30	NR	NR	NR	NR	NR	NR	NR	NR
Di Lorenzo 2010[66]	Cohort 1: Gemcitabine	40	15 Events	NR	NR	15 Events	NR	NR	NR	0 (0)

Trial	Arms	N	Any AE	Any SAE	Treatment-related AE	Any Grade 3-5 AEs	Treatment-related AE Grade 3-5	Treatment-related SAEs	Discontinuation due to any AEs	Death
			n (%)							
	Cohort 2: BCG	40	16 Events	NR	NR	16 Events	NR	NR	NR	1 (2.5)
Bartoletti 2005[117]	Gemcitabine	40	No difference was noted in terms of tolerability in the patients with BCG-refractory disease (P= 0.4863).							
Fiorito 2014[64]	Gemcitabine	41	NR	NR	NR	NR	NR	NR	NR	1 (2.4)
Sternberg 2013[67]	Gemcitabine	69	49 (71)	NR	NR	NR	NR	NR	NR (12)	26 (38)
Gemcitabine / Docetaxel										
Steinberg 2020[118]	Gemcitabine/ Docetaxel	276	112 (40.6)	26 (9.4)	NR	NR	NR	NR	9 (3.3)	44 (16)
Daniels 2020[70]	Gemcitabine/ Docetaxel	59	NR	NR	NR	NR	NR	NR	NR	NR
Steinberg 2015[72]	Gemcitabine/ Docetaxel	45	28 (62)	7 (16)	NR	NR	NR	NR	5 (11)	10 (4.5)
Milbar 2017[71]	Gemcitabine/ Docetaxel (Full Study Population)	33	NR	NR	NR	NR	NR	NR	2 (6)	3 (9)
Caruso 2020[17]	Gemcitabine/Docetaxel	26	NR	NR	NR	NR	NR	NR	NR	NR

AE: adverse event, BCG: bacillus calmette guerin, mg: milligram, n: number, N: total, NR: not reported, rAd-IFN/Syn3: recombinant adenovirus delivered inferferon alpha 2-b with Syn3, SAE: serious adverse event, TRAE: treatment-related adverse event

*Treatment-Emergent

† Six patients (3.8%) died (4 in CIS ± Ta/T1 and 2 in Ta/T1 alone). Five (3%) deaths were during the long-term follow-up period when the patients were off treatment and 1 (1%) was on-study

Table D6. Safety II

Trial	Arms	N	Fatigue	Nausea	Diarrhea	Rash	Urinary Tract Infection	Dysuria	Hematuria	Thrombocytopenia	Urinary Frequency / Urgency
			n (%)								
Nadofaragene Firadenovec											
Phase III[19]	rAd-IFN	157	37 (24)	12 (8)	17 (11)	NR	19 (12)	22 (14)	26 (17)	NR	28 (18)
Phase II SUO-CTC[50]	rAd-IFN 1x10^{11} vps/mL (low-dose)	21	6 (28.6)	3 (14.3)	3 (14.3)	1 (4.8)	3 (14.3)	9 (42.9)	5 (23.8)	NR	NR
	rAd-IFN 3x10^{11} vps/mL (high-dose)	19	7 (36.8)	3 (15.8)	2 (10.5)	1 (5.3)	5 (26.3)	7 (36.8)	5 (26.3)	NR	NR
	Overall	40	13 (32.5)	6 (15)	5 (12.8)	2 (5.1)	8 (20)	16 (40)	10 (25)	NR	16 (40)
Phase I Dinney 2013[51]	Overall	17	NR (47)	NR (35)	NR	NR	NR	NR	NR	NR	NR (88)
Oportuzumab Monatox											
Phase III VISTA[20,52]	Overall	132	17 (13)	14 (11)	16 (12)	NR	43 (32)	34 (26)	33 (25)	NR	20 (15)
Phase II Kowalski 2012[53]	Overall	45	NR	NR	NR	NR	NR	23 (50)	6 (13)	NR	6 (13)
Phase I Kowalski 2010[54]	Overall	64	5 (8)	2 (3)	1 (2)	2 (3)	NR	9 (14)	7 (11)	NR	4 (6)
Pembrolizumab											
Phase II KEYNOTE 057[55,56]	Pembrolizumab 200 mg	96	21 (20.6)	15 (14.7)	22 (21.6)	NR	12 (11.8)	NR	21 (20.6)	NR	NR
Gemcitabine											
Addeo 2010[65]	Gemcitabine	54	NR	NR	NR	NR	NR	5 (9.2)	2 (3.7)	NR	NR
	Mitomycin	55	NR	NR	NR	NR	NR	11 (20)	4 (7.2)	NR	NR
Allchorne 2014[59]	Gemcitabine	19	NR	NR	NR	NR	NR	NR	NR	NR	NR
Gunelli 2007[60]	Gemcitabine	40	NR	NR	NR	NR	NR	37 (93)	0 (0)	NR	NR
Perdona 2010[61]	Gemcitabine	20	NR	NR	NR	NR	NR	2 (10)	NR	1 (5)	NR
Skinner 2013[23]	Gemcitabine	55	NR	NR	NR	NR	NR	NR	NR	NR	NR
Dalbagni 2002[62]	Gemcitabine	18	1 (6)	1 (6)	NR	NR	1 (6)	NR	5 (28)	1 (6)	7 (39)
Dalbagni 2006[22]	Gemcitabine	30	NR	NR	NR	1 (3)	1 (3)	9 (30)	1 (3)	NR	NR
Di Lorenzo 2010[66]	Cohort 1: Gemcitabine	40	NR	2 Events	NR	NR	NR	6 Events	2 Events	2 Events	NR
	Cohort 2: BCG	40	NR	0 Events	NR	NR	NR	8 Events	5 Events	0 Events	NR

Trial	Arms	N	Fatigue	Nausea	Diarrhea	Rash	Urinary Tract Infection	Dysuria	Hematuria	Thrombocytopenia	Urinary Frequency / Urgency
			n (%)								
Bartoletti 2005[117]	Gemcitabine	40	No difference was noted in terms of tolerability in the patients with BCG-refractory disease (p=0.4863).								
Fiorito 2014[64]	Gemcitabine	41	NR	NR	NR	NR	NR	NR	NR	NR	NR
Sternberg 2013[67]	Gemcitabine	69	NR	NR	NR	1 (1.4)	NR	NR	NR	1 (1.4)	25 (36)
Gemcitabine / Docetaxel											
Steinberg 2020[118]	Gemcitabine/ Docetaxel	276	NR	NR	NR	NR	NR	7 (2.5)	2 (0.72)	NR	9 (3.3)
Daniels 2020[70]	Gemcitabine/ Docetaxel	59	NR	NR	NR	NR	NR	NR	NR	NR	NR
Steinberg 2015[72]	Gemcitabine/ Docetaxel	45	NR	3 (7)	NR	NR	1 (2.2)	15 (33)	5 (11)	NR	15 (33)
Milbar 2017[71]	Gemcitabine/ Docetaxel (Full Study Population)	33	4 (12)	NR	NR	NR	NR	NR	3 (9)	NR	Frequency: 7 (21) Urgency: 6 (18)
Caruso 2020[17]	Gemcitabine / Docetaxel	26	NR	NR	NR	NR	NR	NR	NR	NR	NR

BCG: bacillus calmette guerin, mg: milligram, n: number, N: total, NR: not reported, rAd-IFN/Syn3: recombinant adenovirus delivered inferferon alpha 2-b with Syn3

Table D7. Health-Related Quality of Life

Trial	Arm	Timepoint	Patients with CR	FACT-G*	FACT-G* Physical Well-Being Score
Pembrolizumab					
Phase II KEYNOTE 057[58]	Pembrolizumab 200 mg	39 weeks	42	71.1% of patients had improved (≥7 point increase) or stable (change between -7 and +7 points) scores from baseline	77.8% of patients had improved (≥3 point increase) or stable (change between -3 and +3 points) scores from baseline

CR: complete response, FACT-G: Functional Assessment of Cancer Therapy- General, mg: milligram

Table D8. Key Trial Definitions

Trial Details	BCG-Unresponsive	Adequate BCG	Complete Response Rate	High-Grade Recurrence Free Survival
Nadofaragene Firadenovec				
Phase III[19,24,119]	**BCG-Unresponsive:** Patients who did not respond to BCG treatment and have a persistent high-grade recurrence within 12 months after BCG was initiated, or those who despite an initial complete response (CR) to BCG, relapse with high-grade CIS within 12 months of their last intravesical treatment with BCG or relapse with high-grade Ta/T1 NMIBC within 6 months of their last intravesical treatment with BCG	At least 2 previous courses within a 12 month period – defined as at least 5 of 6 induction BCG instillations and at least 2 out of 3 instillations of maintenance, or at least two of six instillations of a second induction course, where maintenance BCG is not given. There is an exception for those who have T1 high-grade disease at first evaluation after induction BCG alone – at least 5 of 6 doses may qualify in the absence of disease progression	No recurrence of high-grade disease using results from urine cytology, cystoscopy, and biopsy of bladder]	No documented recurrence of HG disease or muscle-invasive disease progression
Phase II SUO-CTC[50]	**BCG Refractory:** the inability to achieve a disease-free state at 6 months after adequate induction BCG therapy with either maintenance or reinduction at 3 months.	Adequate induction of BCG was defined as a minimum of five of six treatments, and adequate maintenance was defined as a minimum of two of three treatments	No evidence of recurrence of HG disease at 3, 6, and 9 months; incidence and time to cystectomy; and	Freedom from HG disease recurrence at 12 months, defined by a negative for cause or end of study biopsy

Trial Details	BCG-Unresponsive	Adequate BCG	Complete Response Rate	High-Grade Recurrence Free Survival
	BCG Relapse: recurrence within 1 year after a complete response to adequate BCG treatment		concentration of IFNa-2b in the urine	
Phase I Dinney 2013[51]	Disease recurrence after at least 2 cycles of BCG, with or without recombinant IFN-alpha protein, and a minimum of 3 months since last treatment	2 cycles of BCG therapy as a minimum of one 6-week induction course followed by a 3-week maintenance course	No visual evidence of disease, negative biopsy of the prior scar site (or any visually identified lesion) and negative cytology at 3-month cystoscopy	NR
Oportuzumab Monatox				
Phase III VISTA[52,120]	**BCG-Refractory:** disease which persists at the first evaluation following adequate BCG. Relapsed disease is defined as having a complete response to adequate BCG but recurs at a subsequent evaluation **BCG-Relapsed:** having a complete response to adequate BCG but recurs at a subsequent evaluation	At least 2 courses of BCG: at least one induction and one maintenance course or at least 2 induction courses. The initial induction must be at least 5 treatments within a 7-week period and the second course must be at least 2 treatments within a 6-week period.	No histological evidence of disease and negative urine cytology at the 3-monthy evaluations	NR
Phase II Kowalski 2012[53]	**BCG-Refractory:** Did not achieve disease-free status or had recurrence within 6 months of the last BCG treatment cycle **BCG-Intolerant:** BCG side effects prevented them from completing therapy.	1 or more cycles of BCG in the 24 months before enrollment	No histological evidence of disease and negative urine cytology at the 3-monthly evaluations. Any cases with no histological evidence of disease on initial biopsy but atypical or suspicious urine cytology were also considered CRs only if they remained negative	Assessed by cytology, cystoscopy and, if clinically indicated, biopsies were performed to obtain accurate staging. If no evidence of recurrence of High-Grade disease was detected, then a further dose of rAd-IFN/Syn3 was administered as maintenance therapy. Patients who had recurrence

Trial Details	BCG-Unresponsive	Adequate BCG	Complete Response Rate	High-Grade Recurrence Free Survival
			after being evaluated with repeat biopsy, directed and random.	of High-Grade disease were withdrawn from treatment but were followed for survival and time to cystectomy.
Phase I Kowalski 2010 [54]	**BCG-Refractory:** recurrence within 2 years following at least one complete cycle of BCG	One complete cycle of BCG therapy	Nonpositive urinary cytology and either normal cystoscopy or abnormal cystoscopy with negative biopsy.	NR
Pembrolizumab				
Phase II KEYNOTE 057[55,56]	**BCG-Unresponsive:** Persistent disease despite adequate BCG therapy, disease recurrence after an initial tumor-free state following adequate BCG therapy, or T1 disease following a single induction course of BCG	Administration of at least five of six doses of an initial induction course plus either of: at least two of three doses of maintenance therapy or at least two of six doses of a second induction course.	Negative results for cystoscopy (with TURBT/biopsies as applicable), urine cytology, and computed tomography urography (CTU) imaging	NR
Gemcitabine				
Addeo 2010[65]	NR	NR	NR	NR
Allchorne 2014[59]	**BCG-Recurrence:** failed BCG and developed recurrent tumors despite having been treated for at least 6 weeks. Within this category, patients were categorized at BCG intolerant, persistent, or resistant	6-week induction course	NR	NR
Gunelli 2007[60]	**BCG-Refractory:** Refractory after 6 months of one induction cycle and at least three maintenance cycles	One induction cycle and at least 3 maintenance cycles	**Response:** lack of residual disease at 6 months, certified by cytological and endoscopic examinations	**Event Free Survival:** interval between the date of the first endovesical instillation and the first unfavorable event, superficial disease, progression to infiltrating disease or the

Trial Details	BCG-Unresponsive	Adequate BCG	Complete Response Rate	High-Grade Recurrence Free Survival
				last visit.
Perdona 2010[61]	**BCG-Refractory:** Failure to achieve disease-free state by 6 months after initial BCG therapy with either maintenance or re-treatment at 3 months because of either persistent or rapidly recurring disease	Induction course consisting of 6 weekly instillations and maintenance course of 3 weekly instillations at 3, 6, and 12 months	NR	NR
Skinner 2013[23]	**BCG-Failure:** received and failed more than 2 courses of intravesical BCG within the past 3 weeks	At least two prior courses (one 6-week course, plus one 3-week course, or fewer weeks if BCG was discontinued due to side effects)	Negative cystoscopy with negative biopsy and no evidence of cancer on urine cytology at the week 8-12 cystoscopy	**Recurrence-free survival:** time from registration to first instance of disease recurrence or death from any cause
Dalbagni 2002[62]	NR	NR	Negative posttreatment cystoscopy including a biopsy of the urothelium and negative cytology	NR
Dalbagni 2006[22]	NR	NR	Negative posttreatment cystoscopy including a biopsy of the urothelium and negative cytology	Recurrence-free survival time: time from the date of assessment of response to treatment, to the date of recurrence or last follow-up among patients who achieved a CR.
Di Lorenzo 2010[66]	**BCG-Failure:** whenever muscle-invasive tumor is detected during follow-up, or if a high-grade, non-muscle-invasive tumor is present at both 3 and 6 months, or any worsening of the disease during BCG treatment, as defined by the European Association of Urology	NR	NR	NR

Trial Details	BCG-Unresponsive	Adequate BCG	Complete Response Rate	High-Grade Recurrence Free Survival
Bartoletti 2005[117]	**BCG-Refractory:** recurrence occurred within 6 months of starting BCG treatment	NR	NR	NR
Fiorito 2014[64]	NR	At least a complete induction of BCG	Negative cytology and cystoscopy at 12 months	NR
Sternberg 2013[67]	**BCG-refractory disease:** failure to achieve a disease free state at 6 months following initial BCG therapy with either maintenance or retreatment at 3 months because of a persistent or rapidly growing recurrent tumor **BCG-resistant disease:** recurrence at 3 months following an induction cycle **BCG-relapsing disease:** disease recurrence after the patient was disease free for 6 months **BCG-intolerant disease:** recurrence following administration of a less than adequate course of therapy because of a serious adverse event or symptomatic intolerance that required discontinuation of BCG therapy	NR	No tumor seen at 3 months after treatments and negative cytology results	NR
Gemcitabine / Docetaxel				

Trial Details	BCG-Unresponsive	Adequate BCG	Complete Response Rate	High-Grade Recurrence Free Survival
Steinberg 2020[118]	**BCG-unresponsive**: persistent or recurrent carcinoma in situ (alone or with Ta/T1 disease) within 12 months of adequate BCG, recurrent Ta/T1 disease within 6 months of adequate BCG or high grade T1 disease at first evaluation after induction BCG.	NR	NR	NR
Daniels 2020[70]	NR	NR	NR	Any-grade recurrence: recurrence with low grade papillary carcinoma, high-grade papillary carcinoma, carcinoma in situ (Tis), lamina propria invasion (T1), and any progression beyond these as diagnosed by tissue biopsy after GEM/DOCE induction completion
Steinberg 2015[72]	**BCG refractory:** rapidly recurrent or progressive disease noted at 3 months after diagnosis or persistent disease at 6 months after diagnosis in light of 2 BCG induction courses or induction plus maintenance **BCG relapse:** recurrence after becoming disease free by 6 months **BCG intolerant:** disease recurrence after a less than adequate treatment course due to symptomatic intolerance or a serious adverse event	2 BCG induction courses or induction plus maintenance	NR	NR

Trial Details	BCG-Unresponsive	Adequate BCG	Complete Response Rate	High-Grade Recurrence Free Survival
Milbar 2017[71]	**BCG unresponsive:** patients who did not respond to BCG treatment and have a new (if previously treated for a low-grade NMIBC) or persistent high-grade (HG) recurrence at or around 6 months after BCG was initiated, and those who despite an initial complete response to BCG, relapse with HG NMIBC within 6 months of their last intravesical treatment with BCG. (as defined by 2015 genitourinary cancers symposium task force)	At least 2 courses of BCG: at least 5 of 6 induction instillations and at least 2 of 3 maintenance instillations	NR	Finding of high-grade papillary carcinoma (HgTa), carcinoma in-situ (Tis), lamina propria invasion (T1), and any progression beyond these as diagnosed by tissue biopsy within 6 months of GEM/DOCE induction completion.
Caruso 2020[17]	**NR**	NR	NR	NR

BCG: bacillus calmette guerin, CIS: carcinoma in situ, CR: complete response, HG: high-grade, HgTa: high-grade papillary carcinoma, NR: not reported, rAd-IFN/Syn3: recombinant adenovirus delivered inferferon alpha 2-b with Syn3, Ta: non-invasive papillary tumor, T1: tumor invading subepithelial connective tissue

Appendix E. Comparative Value Supplemental Information

Table E1. Impact Inventory

	Type of Impact (Add additional domains, as relevant)	Included in this Analysis from Health Care Sector Perspective?	Notes on Sources (if quantified), Likely Magnitude & Impact (if not)
Health Outcomes	Longevity effects	X	
	Health-related quality of life effects	X	
	Adverse events	X	
Medical Costs	Paid by third-party payers	X	
	Paid by patients out-of-pocket	No	
	Future related medical costs	X	
	Future unrelated medical costs	No	
Health-Related Costs	Patient time costs	NA	
	Unpaid caregiver-time costs	NA	
	Transportation costs	NA	
Productivity	Labor market earnings lost	NA	
	Cost of unpaid lost productivity due to illness	NA	
	Cost of uncompensated household production	NA	
Consumption	Future consumption unrelated to health	NA	
Social services	Cost of social services as part of intervention	NA	
Legal/Criminal Justice	Number of crimes related to intervention	NA	
	Cost of crimes related to intervention	NA	
Education	Impact of intervention on educational achievement of population	NA	
Housing	Cost of home improvements, remediation	NA	
Environment	Production of toxic waste pollution by intervention	NA	
Other	Other impacts (if relevant)	NA	

NA: not applicable

Adapted from Sanders et al.[77]

Description of evLYG Calculations

The cost per evLYG considers any extension of life at the same "weight" no matter what treatment is being evaluated. Below are the stepwise calculations used to derive the evLYG.

3. First, we attribute a utility of 0.851, the age- and gender-adjusted utility of the general population in the US that are considered healthy.[78]

4. For each cycle (Cycle I) in the model where using the intervention results in additional years of life gained, we multiply this general population utility with the additional life years gained (ΔLYG).

5. We sum the product of the life years and average utility (cumulative LYs/cumulative QALYs) for Cycle I in the comparator arm with the value derived in Step 2 to derive the equal value of life years (evLY) for that cycle.

6. If no life years were gained using the intervention versus the comparator, we use the conventional utility estimate for that Cycle I.

7. The total evLY is then calculated as the cumulative sum of QALYs gained using the above calculations for each arm.

8. We use the same calculations in the comparator arm to derive its evLY.

Finally, the evLYG is the incremental difference in evLY between the intervention and the comparator arms.

Table E2. Additional Model Probabilities* Used for Both CIS ± Ta/T1 and High-Grade Ta/T1 Subgroups

Model Input	Nadofaragene Firadenovec	Oportuzumab Monatox	Hypothetical Comparator	Source
Probability of Transitioning from MIBC to Post-Cystectomy	50.0%	50.0%	50.0%	Gore 2010[83]
Probability of Transitioning from MIBC to Metastatic Disease	3.9%	3.9%	3.9%	Griffiths 2011[84]
Probability of Transitioning from MIBC to Death	4.0%	4.0%	4.0%	Griffiths 2011[84]
Probability of Transitioning from Post-Cystectomy to Metastatic Disease	5.7%	5.7%	5.7%	Shariat 2006[85]
Probability of Transitioning from Metastatic Disease to Death	4.0%	4.0%	4.0%	Gore 2010[83]
Probability of Transitioning from Post-Cystectomy to Death	13.4%	13.4%	13.4%	von der Maase 2005[87]

MIBC: muscle-invasive bladder cancer

*Probabilities are for each 3-month cycle.

Table E3. Administration Cost Inputs

Input	Description	Value	Source
Nadofaragene Firadenovec and Oportuzumab Monatox Administration Costs	Bladder instillation of anticarcinogenic agent (HCPCS code 51720)	$86	CMS.gov[121]
Pembrolizumab Administration Costs	Chemotherapy administration, intravenous infusion technique; up to one hour, single or initial substance/drug (CPT Code 96413)	$143	CMS.gov[121]

Table E4. Results for the Undiscounted Base Case for Nadofaragene Firadenovec and Oportuzumab Monatox Compared to the Hypothetical Treatment in Patients with CIS ± High Grade Ta/T1

Treatment	Total Cost	QALYs	evLYG	Life Years	Time in Progression-Free State (Years)
Nadofaragene Firadenovec*	$347,000	5.94	6.07	7.79	4.45
Oportuzumab Monatox	$346,000	5.33	5.38	7.01	3.54
Pembrolizumab	$303,000	5.79	5.89	7.57	4.23
Gemcitabine ± Docetaxel	$214,000	6.89	7.06	8.73	5.52
Hypothetical Comparator	$223,000	4.94	4.94	6.60	3.04

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

Table E5. Results for the Undiscounted Base Case for Nadofaragene Firadenovec and Oportuzumab Monatox Compared to the Hypothetical Treatment in Patients with High Grade Ta/T1 alone

Treatment	Total Cost	QALYs	evLYG	Life Years	Time in Progression-Free State (Years)
Nadofaragene Firadenovec	$342,000	6.40	6.55	8.18	4.99
Oportuzumab Monatox	$340,000	6.00	6.12	7.72	4.39
Gemcitabine ± Docetaxel	$204,000	6.81	6.98	8.58	5.52
Hypothetical Comparator	$224,000	4.86	4.86	6.49	2.91

*Price for nadofaragene firadenovec and oportuzumab monatox was based on annual price of pembrolizumab

Table E6. Cumulative Net Cost Per Patient Treated with Nadofaragene Firadenovec at Assumed Placeholder Price and Oportuzumab Monatox at Assumed Net Price Over a Five-Year Time Horizon

	Nadofaragene Firadenovec		Oportuzumab Monatox	
Year	Cumulative Cost	Additional Costs per Year (Non-Cumulative)	Cumulative Cost	Additional Costs per Year (Non-Cumulative)
Year 1	$128,296	$128,296	$122,807	$122,807
Year 2	$119,663	-$8,634	$116,033	-$6,775
Year 3	$111,002	-$8,660	$109,572	-$6,461
Year 4	$103,523	-$7,479	$104,370	-$5,202
Year 5	$98,038	-$5,485	$100,919	-$3,450

Table E7. Cost-Effectiveness Threshold Prices per Day for Nadofaragene Firadenovec and Oportuzumab Monatox in Patients with CIS ± Ta/T1

Daily Prices Using…	Annual WAC	Daily Price at $100,000 Threshold	Daily Price at $150,000 Threshold
Nadofaragene Firadenovec			
QALYs Gained	N/A	$312-$329	$448-$472
evLYG	N/A	$343-$361	$495-$520
Oportuzumab Monatox			
QALYs Gained	N/A	$98-$112	$145-$165
evLYG	N/A	$109-$124	$161-$183

QALY: quality-adjusted life year; evLYG: equal value of life years gained; WAC: wholesale acquisition cost; N/A: not available

Table E8. Cost-Effectiveness Threshold Prices per Day for Nadofaragene Firadenovec and Oportuzumab Monatox in Patients with High Grade Ta/T1

Daily Prices Using…	Annual WAC	Daily Price at $100,000 Threshold	Daily Price at $150,000 Threshold
Nadofaragene Firadenovec			
QALYs Gained	N/A	$479-$509	$687-$728
evLYG	N/A	$520-$550	$747-$791
Oportuzumab Monatox			
QALYs Gained	N/A	$312-$342	$451-$495
evLYG	N/A	$340-$373	$494-$541

QALY: quality-adjusted life year; evLYG: equal value of life years gained; WAC: wholesale acquisition cost; N/A: not available

Appendix F. Public Comments

This section includes summaries of the public comments prepared for the Midwest CEPAC Public Meeting on November 20, 2020. These summaries were prepared by those who delivered the public comments at the meeting and are presented in order of delivery.

A video recording of all comments can be found here. Conflict of interest disclosures are included at the bottom of each statement for each speaker who is not employed by a pharmaceutical manufacturer.

Tom Cannell, DVM, Sesen Bio
President & Chief Executive Officer

Oportuzumab monatox has a dual mechanism of action (MOA) which is unique and differentiated from other intravesical therapies. As a primary MOA, Oportuzumab monatox specifically binds to and kills bladder tumor cells. As a secondary MOA, dying tumor cells display immunogenic cell death signals and release neo-antigens which are known to promote an anti-tumor immune response potentially leading to long-term responses.

Sesen Bio believes that the Phase 3 Oportuzumab monatox study demonstrated a clinically meaningful benefit for BCG-unresponsive NMIBC patients and a favorable safety and tolerability profile with only a 3% discontinuation rate. Oportuzumab monatox showed strong primary endpoint data for complete response rate and duration of response. Also, important secondary endpoints including the potential to significantly delay radical cystectomy and the compelling overall survival data differentiate Oportuzumab monatox from other intravesical therapies. An estimated 76% of patients were cystectomy-free at 3 years. Moreover, responders had an 88% probability of remaining cystectomy-free at 2 years versus 61% for non-responders. The 2-year survival rate of patients on trial was 96% compared to 94% for the general population of similar age and gender demographics. In the end, these benefits make a huge difference to the lives of patients who have been through a long and arduous journey since being diagnosed with bladder cancer.

Taken together, Oportuzumab monatox showed a favorable risk benefit profile for the treatment of BCG-unresponsive NMIBC. Sesen Bio believes that these data will lead to the strong advocacy of payers and physicians.

Dr. Tom Cannell is a full-time employee of Sesen Bio.

Vijay Kasturi, MD, FerGene, Inc.
Vice President, Medical Affairs; Interim Lead – Clinical Development

Currently there exist critical unmet needs for patients with BCG unresponsive high-grade non-muscle invasive bladder cancer (HG NMIBC). These patients who are often elderly with comorbidities are either ineligible or frequently refuse to have radical cystectomy due to the significant morbidity, detriment on patient's health, quality of life, sexual and psychosocial functions, and not-insignificant mortality. Existing bladder preserving therapies are few and unsuccessful in many patients, highlighting the need for new bladder preserving therapies.

Nadofaragene firadenovec is a novel innovative bladder preserving gene therapy that reported the highest initial response rates among the 3 new agents (nadofaragene firadenovec, oportuzumab monatox, pembrolizumab) evaluated by ICER. The initial CR/HG RFS rates are 53.4% for CIS ± Ta/T1 patients and 72.9% for HG Ta/T1 patients. The durability of response among patients who achieved CR/HG-RFS is 41% in CIS ± Ta/T1 and 51% in HG Ta/T1 at 18 months. Both the high response rates and the durability of response have exceeded the clinically meaningful thresholds set by the expert consensus panel informing the FDA bladder cancer guidance for this difficult-to-treat patient population. It also demonstrated the lowest number of grade 3-5 AEs, serious AEs, and discontinuation due to AEs among the 3 new treatments, with no treatment-related deaths. The trial is conducted by the Society of Urological Oncology Clinical Trials Consortium (SUO-CTC) and is the only agent with results published in the top-tier peer-reviewed journal, Lancet Oncology, further validating its clinical importance and scientific rigor.

Nadofaragene firadenovec is administered once every three months, the least frequent among the 3 new agents which could potentially offer economic and quality of life benefits including less frequent office visits, less disruption to patients' daily lives, higher work productivity and income, and less caregiver burden.

ICER's evaluation of nadofaragene firadenovec is very timely. Its cost-effectiveness assessment, however, fell short on a number of critical aspects and substantially underestimated the cost-effectiveness of nadofaragene firadenovec. Specifically, ICER assumed that patients are more likely to lose response when treated with nadofaragene firadenovec after month 12 than when treated with pembrolizumab (12.3% vs. 7.8%), in direct contradiction to the observed trial data where, based on the most recent data readout, patients are less likely to lose response when treated with nadofaragene firadenovec than with pembrolizumab (5.9% vs. 7.8%). This observed long-term durability of response data should be used instead of assumptions. Additionally, ICER used less robust methodology to extrapolate the long-term clinical probabilities after year 1. ICER only used two selected data points, and arbitrarily applied an exponential model. Had the full set of available data and an appropriate methodology (generalized gamma model) been used, the incremental cost-effectiveness ratio for nadofaragene firadenovec in the CIS±Ta/T1 population could have been reduced by 60%.

ICER's evaluation used treatment-specific progression estimates based on inconsistent methodology and overestimated the risk of progression associated with nadofaragene firadenovec. Specifically, ICER's approach assumed that all progression events from the Phase 3 trial occurred within 12 months, while in fact, these events occurred over a median follow-up of 20 months. Consequently, ICER's current assessments considered nadofaragene firadenovec was associated with a higher risk of progression than pembrolizumab in the CIS±Ta/T1 population and oportuzumab monatox in the HG Ta/T1 population. If ICER used consistent approach to analyze the progression data, nadofaragene firadenovec would be predicted to have comparable or lower risk of progression compared to these two treatments.

ICER used response measures derived with inconsistent method for oportuzumab monatox and nadofaragene firadenovec in the HG Ta/T1 population, resulting in significant underestimation of the efficacy for nadofaragene firadenovec. Had ICER used a consistent method, the proportion of patients who remained in response at month 12 would increase by 38% for nadofaragene firadenovec, resulting in higher QALY estimates than for oportuzumab monatox.

ICER assumed away some serious AEs in the oportuzumab monatox and pembrolizumab cost-effectiveness assessment. Specifically, the pembrolizumab trial reported 29.4% of patients experienced grade 3-5 AE, including many severe immune-mediated AEs. The oportuzumab monatox trial reported 21.1% of patients with grade 3-5 AEs, including acute kidney injury, intestinal obstruction, and serious urinary tract infections. These events have major cost and quality of life impact and were not captured in ICER's economic evaluation.

We urge ICER to incorporate accurate measures/data and apply consistent methodology in its cost-effectiveness assessment across products in its final report. Nadofaragene firadenovec is a highly valuable new treatment option for HG NMIBC BCG unresponsive patients who are in critical need for new treatment options to fill the current gap in care and improve patient outcomes.

Dr. Vijay Kasturi is a full-time employee of FerGene, Inc.

Yair Lotan, MD, UT Southwestern Medical Center at Dallas
Professor, Chief of Urologic Oncology

Patients with high grade non-muscle invasive bladder cancer who are unresponsive to BCG face a challenging dilemma. They are at risk for progression and death from bladder cancer. However, the most effective therapy which is to remove the bladder (cystectomy) results in life-long reduction in quality of life and a high rate of morbidity as well as risk for mortality. The current alternative options include intravesical chemotherapy either FDA approved (Valrubicin) or non-approved (gemcitabine +/- docetaxol) and systemic immune therapy (pembrolizumab). The option of conservative management or observation is ineffective and not one that patients willingly pursue.

There are 2 new potential therapies under evaluation by ICER including nadofaragene firadenovec and vicinium. I focused my remarks regarding nadofaragene firadenovec since I participated in the phase II and III clinical trials and am familiar with the data and have treated patients with this therapy. I have also published on cost-effectiveness and am aware of the challenges with accurately modeling outcomes since assumptions are necessary to create models and there is often insufficient data to create ideal models. From this perspective it is important to develop as accurate a picture as possible since the results of cost-effectiveness models have practical implications for patients if payers make decisions regarding drug availability based on these results.

There were several areas that the ICER modeling made assumptions regarding outcomes that deserve comments. One of the main advantages of nadofaragene is the high degree of safety conferred by this intravesical therapy. Less than 5% of patients experienced grade 3–4 drug-related adverse events and there were no treatment-related deaths. By comparison, pembrolizumab therapy is a systemic therapy and 12.7% of patients had grade 3–4 treatment-related adverse events and over 20% of patients experience immune-related adverse events (colitis, pneumonitis, and hypothyroidism). ICER's cost-effectiveness assessments did not include the costs or quality of life implications of some of these toxicities which could have significant cost-effectiveness implications. Furthermore, there are practical implications since these risks can affect patients' willingness to undergo these treatments, so it is important to have other effective options available to them.

Another area that has a significant impact on cost-effectiveness is in assumptions regarding long-term effectiveness. Since the model is multiple years durations, assumptions regarding risk of recurrence and progression in years 2-5 can have a significant impact on overall outcomes. For their modeling ICER used more unfavorable likelihood of maintaining response than what is observed in the clinical trial of nadofaragene firadenovec in its latest data readout with 24-month follow-up, and substantially underestimated the cost-effectiveness of nadofaragene firadenovec as a result. In contrast, ICER used long term data with more mature follow-up observed in keynote 57 trial for pembrolizumab. This may in part be related to how each trial captured events. There was

also a mandatory biopsy at 12 months in the nadofaragene trial and not the keynote 57 trial which can lead to a bias in relation to recurrence and progression in favor of pembrolizumab.

One other comparison made by ICER was in relation to gemcitabine and docetaxol. I have treated many patients with this combination of intravesical chemotherapy agents and agree that they can be effective in some patients with BCG unresponsive disease. In the ICER modeling the strategy of using gemcitabine/docetaxol dominates every scenario and an uninformed observer may wonder why it is not the preferred choice for all patients with BCG unresponsive disease. I highlighted that the data regarding effectiveness of gemcitabine/docetaxol is primarily from retrospective studies where less than 40% of the patients met criteria for BCG unresponsiveness according to the FDA and the median follow up was less than 1 year. There are considerable biases associated with retrospective studies and comparing the level of evidence of this data with prospective trials can lead to inaccurate conclusions.

At the end of the day, patients with BCG unresponsive disease need effective options and some will likely prefer to try one or 2 different therapies prior to undergoing cystectomy. Nadofaragene represents an important therapeutic option for patients with BCG unresponsive non-muscle invasive bladder cancer.

Dr. Yair Lotan has received consulting fees from AbbVie, FerGene and Bristol Myers Squibb. Dr. Lotan was a research participant with FKD trials.

Appendix G. Conflict of Interest Disclosures

Tables G1 through G3 contain conflict of interest (COI) disclosures for all participants at the November 20, 2020 Public meeting for Midwest CEPAC.

Table G1. ICER Staff and Consultants and COI Disclosures

ICER Staff and Consultants	
Steven J. Atlas, MD, MPH* Director, Primary Care Research & Quality Improvement Network, Massachusetts General Hospital; Associate Professor of Medicine, Harvard Medical School	**Monica Frederick**,* Program and Event Coordinator, ICER
Molly Beinfeld, MPH,* Research Lead, Evidence Synthesis, ICER	**Avery McKenna,*** Research Assistant, ICER
Rick Chapman, PhD, MS,* Director of Health Economics, ICER	**Steven D. Pearson, MD, MSc,*** President, ICER
Mrinmayee Joshi B. Pharm, PhD Student University of Illinois at Chicago College of Pharmacy	**David M. Rind, MD, MSc,*** Chief Medical Officer, ICER
Maggie O'Grady,* Program Manager, ICER	**Daniel R. Touchette, PharmD, MA*** University of Illinois at Chicago College of Pharmacy

*No conflicts of interest to disclose, defined as individual health care stock ownership (including anyone in the member's household) in any company with a product under study, including comparators, at the meeting in excess of $10,000 during the previous year, or any health care consultancy income from the manufacturer of the product or comparators being evaluated.

Table G2. Midwest CEPAC Panel Member Participants and COI Disclosures

Participating Members of Midwest CEPAC	
Eric Armbrecht, PhD (Chair)* Associate Professor, Saint Louis University Center for Health Outcomes Research, School of Medicine and College for Public Health & Social Justice	**Yngve Falck-Ytter, MD, AGAF*** Professor of Medicine, Case Western Reserve University; Chief, Gastroenterology and Hepatology VA Northeast Ohio Healthcare System, Cleveland
Alan Balch, PhD* Chief Executive Officer, Patient Advocate Foundation, National Patient Advocate Foundation	**Bradley Martin, PharmD, PhD*** Professor, Division of Pharmaceutical Evaluation and Policy, University of Arkansas for Medical Sciences College of Pharmacy
Bijan Borah, PhD* Professor of Health Services Research, Mayo Clinic College of Medicine and Science	**Timothy McBride, PhD*** Co-Director, Center for Health Economics and Policy; Professor, Brown School, Washington University in St. Louis
Angela Brown, MPH* Chief Executive Officer, St. Louis Regional Health Commission (RHC)	**Scott Micek, PharmD*** Associate Professor, Pharmacy Practice, St. Louis College of Pharmacy
Kelly Buckland, MS* Executive Director, National Council on Independent Living	**Reem Mustafa, MD, MPH, PhD*** Associate Professor of Medicine, Division of Nephrology and Hypertension, and Director, Outcomes and Implementation Research, University of Kansas Medical Center
Aaron Carroll, MD, MS* Professor of Pediatrics; Associate Dean for Research Mentoring; Director, Center for Health Policy and Professionalism Research, Indiana University School of Medicine	**Rachel Sachs, JD, MPH*** Associate Professor of Law, Washington University in St. Louis
Stacie B. Dusetzina, PhD* Associate Professor of Health Policy, Ingram Associate Professor of Cancer Research, Vanderbilt University School of Medicine	**Kurt Vanden Bosch, PharmD*** System Formulary Manager, St. Luke's Health System, Idaho

*No relevant conflicts of interest to disclose, defined as more than $10,000 in healthcare company stock or more than $5,000 in honoraria or consultancies during the previous year from health care manufacturers or insurers.

Table G3. Policy Roundtable Participants and COI Disclosures

Policy Roundtable Participant	Conflict of Interest
Stephanie Chisolm, PhD, Director of Education and Research, Bladder Cancer Advocacy Network	BCAN receives funding from FerGene and Merck.
Rachelle Dillon, PhD, Director, Clinical Operations, Sesen Bio	Dr. Rachelle Dillon is a full-time employee for Sesen Bio.
Leslie Fish, RPh, PharmD, Vice President of Clinical Pharmacy, IPD Analytics	Dr. Leslie Fish is a full-time employee of IPD Analytics.
John Gore, MD, MS, FACS, Associate Professor, Department of Urology; Adjunct Associate Professor, Department of Surgery, University of Washington	Dr. John Gore is an investigator for research sponsored by FerGene Pharmaceuticals unrelated to this review.
John W. McKnight, PharmD, BCPS, Vice President, HPS Clinical and Specialty Strategies, Humana	Dr. McKnight is a full-time employee of Humana.
Aaron Mitchell, MD, MPH, Assistant Attending, Medical Oncologist, Memorial Sloan Kettering Cancer Center	Dr. Aaron Mitchell has no financial conflicts to disclose.
Karen Sachse, RN, MSN, Patient Advocate	Karen Sachse has received honorarium for participating in a patient focus group for FerGene.
Kristen Wachsmuth, DHSc, MBA, Senior Director, Medical Affairs & Clinical Development, FerGene	Dr. Kristen Wachsmuth is a full-time employee of FerGene.