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

Draft Evidence Report

September 17, 2020

Prepared for

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None of the above authors disclosed any conflicts of interest.

How to cite this document: Atlas SJ, Touchette DR, Beinfeld M, McKenna A, Joshi M, Chapman R, Pearson SD, Rind DM. Nadofaragene Firadenovec and Oportuzumab Monatox for BCG-Unresponsive, Non-Muscle Invasive Bladder Cancer: Effectiveness and Value; Draft Evidence Report. Institute for Clinical and Economic Review, September 17, 2020. https://icer-review.org/material/bladder-cancer-draft-evidence-report/

DATE OF PUBLICATION: September 17, 2020

Steve 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. Steve Atlas and Molly Beinfeld authored the chapter describing what ICER learned from patients (Chapter 2 Patient Perspectives). Dan 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 Steve Pearson provided methodologic guidance on the clinical and economic evaluations.

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The funding for this report comes from government grants and non-profit foundations, with the largest single funder being the Laura and John Arnold Foundation. 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 http://www.icer-review.org/about/support/.

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In the development of this report, ICER's researchers consulted with several clinical experts, patients, manufacturers and other stakeholders. The following clinical experts provided input that helped guide the ICER team as we shaped our scope and report. None of these individuals is responsible for the final contents of this report or should be assumed to support any part of this report, which is solely the work of the ICER team and its affiliated researchers.

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

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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

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.[7] 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.[8] It is rare in those younger than 40 years old and diagnosis is most common in the late sixties or early seventies.[9] 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.[10] 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).[11] 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%).[12] 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.[13] 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.[14] 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.[11] Instillations of chemotherapeutic agents such as gemcitabine (an antimetabolite) either alone or alternating with another chemotherapeutic agent (docetaxel, a taxane) are commonly used,[15] 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.[16]

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.[15]

Interventions

Nadofaragene Firadenovec

Nadofaragene firadenovec (Adstiladrin®) uses a nonreplicating recombinant adenovirus vector that encodes the human interferon alfa-2b gene.[17] 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.[18] 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.

Oportuzumab Monatox

Another new target for intravesical treatment is the epithelial cell adhesion molecule (EpCAM) positive cancer cell.[19] 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.[20] 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.

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).[21]

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.[15] 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.[15,22] A fourth group includes patients with persistent or recurrent CIS within 12 months for whom two courses of BCG (or adequate BCG) have failed.[23] 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.[24] 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:[25]

- **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.[22] 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.[22] 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 public comments on our draft scoping document from two patient advocacy groups and a patient 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, insurers have not released coverage policies for these new therapies. We do not believe that coverage policies for the comparator treatments assessed in this review will serve as models for coverage of nadofaragene firadenovec and oportuzumab monatox, which utilize unique mechanisms of action, so we have not summarized policies for these treatments.

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[26]

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[27]

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[28]

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.[29,30] We conducted the review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[31] 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).[32]

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 955 potentially relevant references (see Appendix Figure A1), of which 26 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 26 references, three 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 four references represented four studies of gemcitabine in combination with docetaxel.

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).[33-35] 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 interim results from NCT02773849, a Phase III, US-based, open-label, single-arm trial.[33] 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.[33] Most patients (96%) received at least two previous courses of BCG treatment within a 12-month period.[36] 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. At the

time of this report, only interim results were available from the Phase III study, which we supplemented with data from conference abstracts and data provided by the manufacturer.

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.[34] 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.[35]

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 inferferon 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)[33]. 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 6, 9, and 12 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[33].

Table 4.2. Efficacy Outcomes for Nadofaragene Firadenovec

Trial	Time Point: Months	3	6	9	12
Phase III NCT02773849	**Complete Response, n (%)**				
	Overall (N=151)	90 (59.6)	NA	NA	NA
	CIS ± Ta/T1 (N=103)	55 (53.4)	NA	NA	NA
	HG Ta/T1 alone (N=48)	35 (72.9)	NA	NA	NA
Phase III NCT02773849	**High-Grade Recurrence Free Survival, n (%)**				
	Overall (N=151)	90 (59.6)	72 (47.7)	64 (42.4)	46 (30.5)
	CIS ± Ta/T1 (N=103)	55 (53.4)	42 (40.8)	36 (35.0)	25 (24.3)
	HG Ta/T1 alone (N=48)	35 (72.9)	30 (62.5)	28 (58.3)	21 (43.8)
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)

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)

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) by 12 months. 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.[33] 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 ten (70.1%) reported some AE, of which 6 (3.8%) were grade 3-5 and 3 (1.9%) were serious. The most commonly reported drug-related AE was irritative voiding symptoms. Serious events included one case each of syncope, sepsis, and hematuria. Three patients (1.9%) discontinued due to a treatment-emergent AE (TEAE); no deaths were reported.[33,36]

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

Adverse Events	n (%)
Any AE	110 (70.1)
Grade 3-5 AE	6 (3.8)
Serious AE	3 (1.9)
Death	0 (0)
Discontinuation due to TEAE	3 (1.9)
Discontinuation due to Serious AE	NR

AE: adverse event

Trials of Oportuzumab Monatox

We identified three single-arm trials of oportuzumab monatox that met our inclusion criteria (Table 4.4).[37-39] 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.[37] 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 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)[38] 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.[39] 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**	30mg 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	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%) 65 (49%) had 2 prior BCG courses; 68 (51%) 3 or more courses; 65 (49%) had 2 prior BCG courses; 68 (51%) 3 or more courses
NCT00462488 **N=45** **Phase II open-label single arm**	30mg 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, a CR was achieved in 36 (40%) at three months. CR rates were 28%, 21%, and 17% at six, nine, and 12 months, respectively.[37] In the Phase II trial, 18 of 45 (40%) patients in the overall study population achieved CR at three months.[38] 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.[39]

High-Grade Recurrence Free Survival

In the VISTA trial, HGRFS in the overall study population was 50%, 40%, 31%, 29% and 21% at 3, 6, 9, 12, and 24 months, respectively (Table 4.5). For the CIS ± Ta/T1 group, HG-RFS was 42%, 32%, 22%, 20%, and 13% at three, six, nine, 12, and 24 months. For the HG Ta/T1 group, HGRFS was 69%, 59%, 53%, 50%, and 37% at three, six, nine, and 12 months.[40] 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 (%)**						
	Overall (N=133)	NA	NA	NA	NA	NA	NA
	CIS ± Ta/T1 (N=89)	36 (40.0)	25 (28.0)	19 (21.0)	15 (17.0)	NA	287 days (±154) (9.6 months)
	Ta/T1 alone (N=40)	NA	NA	NA	NA	NA	402 days (13.4 months)
	High-Grade Recurrence Free Survival, n (%)						
	Overall (N=133)	NR (50.0)	NR (40.0)	NR (31.0)	NR (29.0)	NR (21.0)	NR
	CIS ± Ta/T1 (N=93)	NR (42.0)	NR (32.0)	NR (22.0)	NR (20.0)	NR (13.0)	NA
	HG Ta/T1 alone (N=40)	NR (69.0)	NR (59.0)	NR (53.0)	NR (50.0)	NA (37%)	NA

Trial	Time Point (Months)	3	6	9	12	24	Duration of response, Median (95% CI)
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)

Other outcomes, such as progression to MIBC, were not reported in any trial we identified of oportuzumab monatox.

Harms of Oportuzumab Monatox

As of the 12-month data output (05/29/2019 data cut-off), 117 patients (88%) reported any AE. The most common AEs were urinary tract infection (32%), pain or burning on urination (26%), hematuria (25%), and urinary frequency (17%). Twenty-eight patients (21%) experienced grade 3-5 AEs and 19 (14%) were classified as serious. The most common SAEs were acute kidney injury (2%), intestinal obstruction (2%), and serious hematuria or urinary tract infection (4%). Five patients (3.8%) discontinued due to an AE or SAE. One death (<1%) was reported by the manufacturer.[41]

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

Adverse Events	n (%)
Any AE	117 (88)
Grade 3-5 AE	28 (21)
Serious AE	19 (14)
Death	1 (<1)
Discontinuation due to any AE	5 (3.9)

AE: adverse event, n: number

Comparators

Trials of Pembrolizumab

Phase II KEYNOTE 057

Evidence to inform our assessment of pembrolizumab was mainly derived from Keynote 057 (Table 4.7).[42,43] 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.[44]

Table 4.7. Trials of Pembrolizumab[43]

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	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: total 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 24 months, respectively.[45]

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.[42,43]

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,[46] 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[43,45]

Trial	Time Point: Months	3	6	9	12	24	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[43]

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 an 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.[44] 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[43,44]

Adverse Events	Patients, n (%)	
	Cohort A (N=102)	Pembrolizumab Reference Safety Dataset (N=2799)
Any AE	99 (97.1)	2727 (97.4)
Grade 3-5 AE	30 (29.4)	1273 (45.5)
Serious AE	26 (25.5)	1042 (37.2)
Death	2 (2.0)	110 (3.9)
Discontinuation due to any AE	14 (13.7)	587 (20.9)
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

Trials of Gemcitabine with and without Docetaxel

Gemcitabine

We identified 11 trials of gemcitabine, of which eight were single-arm prospective trials,[47-54] two were randomized controlled trials (RCTs)[55,56] comparing gemcitabine to another agent (mitomycin or BCG), and one was a retrospective chart review (Table 4.10).[57] 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,[47,48,55,56] 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.[50-52] 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 (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
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
Di Lorenzo 2010 N=40	2,000 mg 2x/week for 6 weeks then 1x/week for 3	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)

Trials	Dose(s) Evaluated	Inclusion Criteria	Outcomes	Baseline Characteristics
Phase II RCT gemcitabine vs. BCG	weeks every 3 months			• 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.[52] In Skinner 2013, 28 out of 47 (60%) study participants had CIS and the study reported a 40% CR at three months.[58] In Perdona 2010, 7 out of 20 (35%) study participants had CIS and the study reported a 75% CR at three months.[49] Two studies, one

prospective and one retrospective reported CR outcomes but did not specify a time point.[51,57] 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.[59]

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).[49,50,52] For patients with CIS ± Ta/T1, RFS varied greatly from study to study, from 54% at three months[50] to 93% at three months[52] (Table 4.11). RFS declined precipitously over time, with studies reporting 21% to 50% RFS at 12 months [50,52] and 15% to 38% RFS at 24 months.[49,52]

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).[55] In another study with a similar population, RFS was 95%, 82%, and 66% at six, 12, and 24 months, respectively.[48]

One study reported a 42% HGRFS rate at 12 months in patients with high-grade Ta/T1 disease.[47]

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).[49,50] 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).[47] One study that did not specify the tumor grades of the study participants[59] 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.[59]

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).[60-63] 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.[64]

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).[60-62] 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.[60] 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.[61,62] 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).[63]

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.[60] At two years, 11 patients (4%) 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[62], 9% at 15 months[63], and 4% at two years.[60]

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%[56], 39%[55], 67%[50], and 71%.[57] The most common AEs were dysuria (9-30%),[49,52,55] hematuria (3-28%),[51,52,55] and urinary tract infection (3-6%).[51,52] One study reported that 12% of patients discontinued treatment due to AEs.[57]

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.[60] 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.[65]

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 %						
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)						
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: total, 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.[65,66] 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. The primary outcome of nadofaragene firadenovec and oportuzumab monatox was CR 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. 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

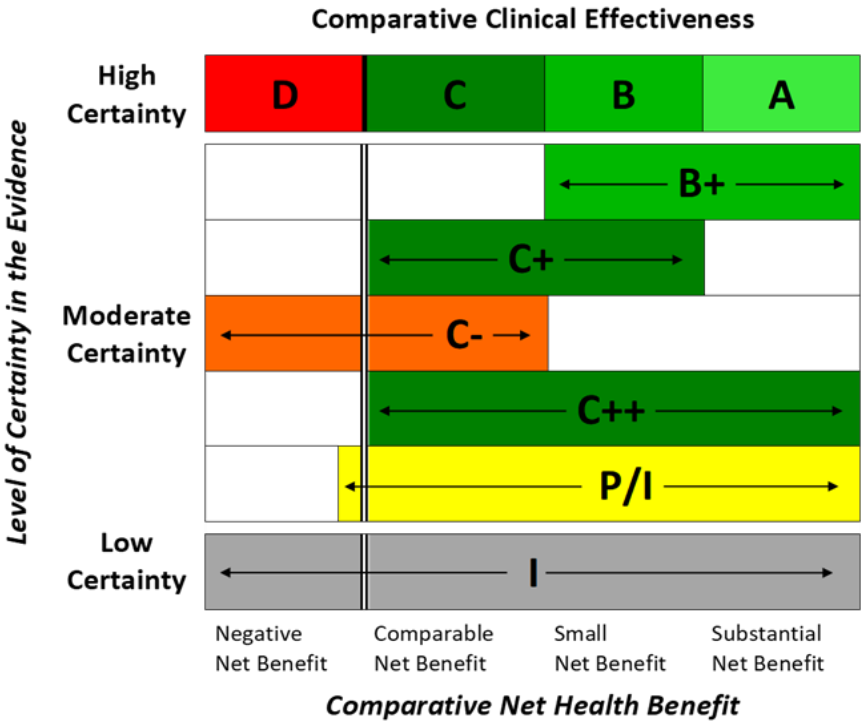
uncertainty about their efficacy over time. This is particularly important in that most patients receiving nadofaragene firadenovec or oportuzumab monatox either did not have a CR or had recurrence/progression over time. Few patients progressed to metastatic disease or died during the short follow-up 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 (but nonzero) likelihood of a negative net health benefit*
I = "Insufficient" – *Any situation in which the level of certainty in the evidence is low*

Table 4.16. Summary of Efficacy and Harms of Nadofaragene Firadenovec, Oportuzumab Monatox, Pembrolizumab, and Gemcitabine ± Docetaxel

Trial	Intervention	Population	CR at 3 months, n (%)	HGRFS at 12 months, n (%)	Median Duration of response	Discontinuation due to any AE
Phase III	Nadofaragene firadenovec	Overall	59.6%	30.5%	NR	1.9%
		CIS± HG Ta/T1	53.4%	24.3%	NR	
VISTA	Oportuzumab monatox	Overall	NR	29%	NR	3.8%
		CIS± HG Ta/T1	40%	20%	287 days (9.6 months)	
Keynote 057	Pembrolizumab	CIS± HG Ta/T1	40.6%	NR	16.2 months	9.8%
Dalbagni 2006 and Skinner 2013	Gemcitabine	Overall*	40-50%	21-28%**	3.6 -6.1 months	12%***
Steinberg 2020	Gemcitabine with Docetaxel	Overall*	NR	60-69%†	NR	9.4%††

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

*Includes mixed study populations of CIS ± HG Ta/T1 and Ta/T1 disease only not reported separately

**Includes recurrence of any type (not just HG)

***Discontinuation due to AEs not reported in Dalbagni 2006 and Skinner 2013; estimate provided from Sternberg 2013

†Lower bound of HGRFS estimate range is for CIS ± HG Ta/T1 population; upper bound is Ta/T1 disease only

††Indicates percentage of patients whose treatment schedule was affected by side effects

Results from studies of the interventions and comparators of interest are presented in Table 4.16. 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. 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. In addition, uncertainties caused by lack of comparator arms in the studies, varied patient populations and histologies, differences in prior treatments, 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.

As such, we have rated both nadofaragene firadenovec and oportuzumab monatox as "comparable or incremental" ("C+") when compared with best supportive care, given the possibility of benefits

and the likelihood that serious harm is unusual. 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 4.17.

Table 4.17. 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)

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. The first population was patients with CIS ± HG Ta/T1 (population 1) and the second population were 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 usual care were generated. We also calculated the incremental cost effectiveness of pembrolizumab and gemcitabine ± docetaxel compared with usual care.

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.[67]

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 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 hypothetical subgroups of patients with BCG-unresponsive NMIBC: those with 1) CIS ± HG Ta/T1 and 2) HG Ta/T1 alone. In the model, patients in Group 1, with CIS ± Ta/T1 NMIBC, were treated with nadofaragene firadenovec or oportuzumab monatox. Pembrolizumab and gemcitabine ± docetaxel were included in the model for patients in Group 1, but not directly compared with nadofaragene firadenovec or oportuzumab monatox. Usual care was the comparator for all treatments. Patients in Group 2, with HG Ta/T1 alone, were treated with nadofaragene firadenovec or oportuzumab monatox. Gemcitabine ± docetaxel was included in the model for patients in Group 2, but not directly compared with nadofaragene firadenovec or oportuzumab monatox. The comparator for all treatments was usual care. For both NMIBC subgroups, usual care was intentionally left undefined. The effectiveness of this comparator in achieving CR and maintaining high-grade recurrence free survival was varied, using a rate ratio, from CR and high-grade recurrence free survival at three months of 0% to the probability of achieving CR and high-grade recurrence free survival with the most effective treatment from clinical trials.

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 usual care. Patients transitioned from "Initial Treatment" to "Complete Response/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 "Complete Response/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 "Complete Response/Disease-free" to "MIBC." Similarly,

we restricted the transition from "Complete Response/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.[68] In addition, cystectomy and short-term mortality costs were accrued during transitions to "Post-cystectomy" and "Death," respectively.

Figure 5.1. Model Framework

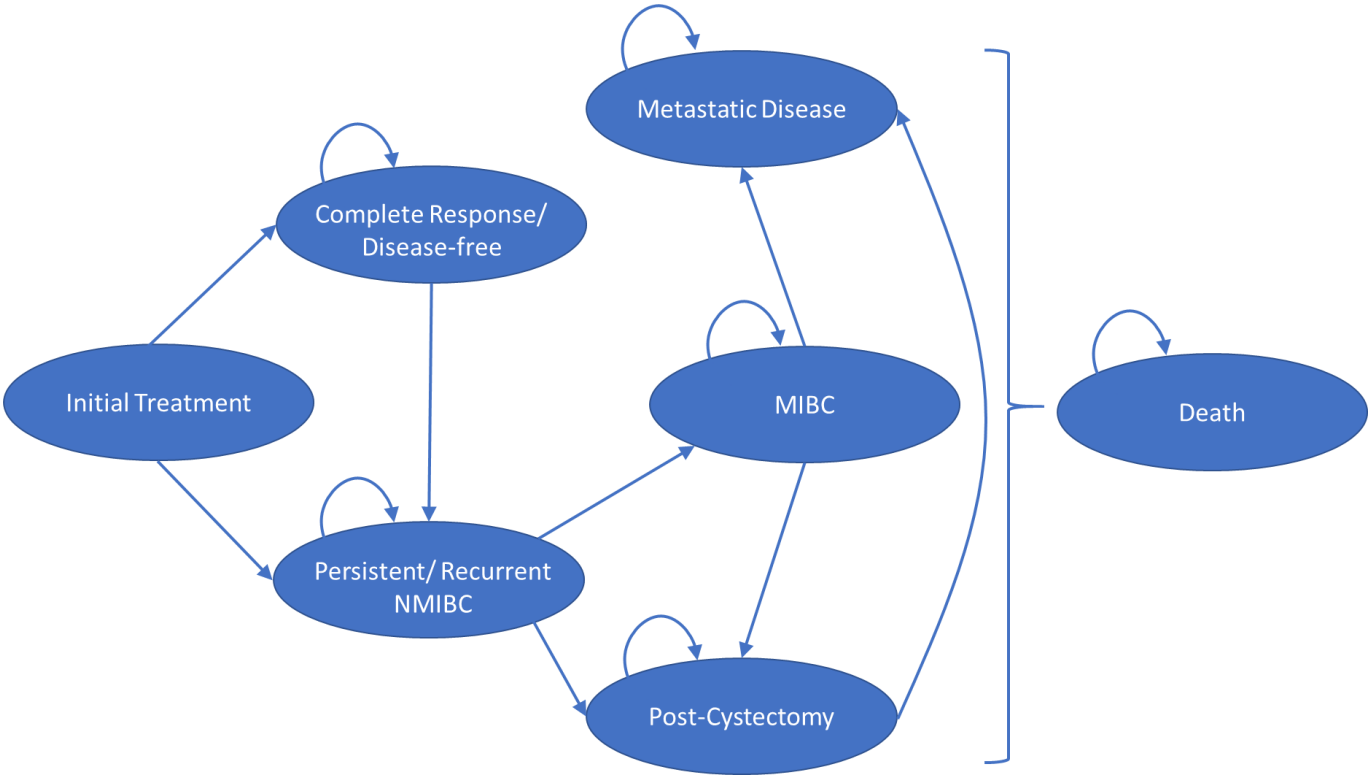


Table 5.1. Treatment Response Definitions Used in the Model

Treatment Response Description	Definition	Calculation from Clinical Trials
Complete Response/ 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.	Proportion of all patients who were and remained disease-free at defined time points. May also be reported as "recurrence-free survival."
Persistent or Recurrent NMIBC	Persistent is 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 is 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 recurrence- or persistence-free survival (i.e. 1 – recurrence-free survival).
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

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[36] Sesen Bio data on file[40] Stuart 2019[69]
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 [redacted],[36] and oportuzumab monatox, 30 mg given intravesically twice weekly for six weeks then once weekly thereafter with a mean treatment duration of 8.1 months.[70] 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.[60] 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, usual care was intentionally left undefined. For the base case, the effectiveness of usual care was set to a CR probability of 0%. The effectiveness of usual care 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.	To date, we have been unable to identify utilities for metastatic disease specifically due to bladder cancer. If updated utility data become available, we will remove this assumption.
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 longer period.	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.[40,60,69,71] The effectiveness of gemcitabine ± docetaxel was obtained from a large multicenter noncomparative retrospective evaluation.[60] 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.[61,64,72] 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).[61,62,64]

The effectiveness of usual care 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 "Complete Response/Disease-free." The inverse of the same risk ratio was applied to modify the probabilities associated with transitions from "Complete Response/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 zero and one resulted in the effectiveness of usual care varying between completely ineffective to having the same benefit as the most effective treatment. However, because usual care is a hypothetical treatment, the costs and disutility associated with adverse events were not included. The base-case value for the risk ratio was zero.

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.[40,60,69,73] The probability of moving from "Complete Response/Disease-free" to "Persistent/Recurrent NMIBC" was determined from HGRFS survival at six, nine, and 12 months and were time varying. The probability of HGRFS at either 12 or 24 months, whichever time period was greater and available from clinical trials, was 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.

Transitions directly from "Complete Response/Disease-free" to "MIBC" were not allowed in the model; all transitions to the "MIBC" state occurred from "Persistent/Recurrent NMIBC." 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 – HGRFS), and then adjusting for three-month cycles. Since progression-free survival was not available for pembrolizumab and the resulting value was extremely similar for nadofaragene firadenovec and oportuzumab monatox, the average value for nadofaragene firadenovec and oportuzumab monatox was used for all treatments. 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.[74,75] Transitions from "MIBC" to "Metastatic Disease" and "Death" were obtained from a large

collaborative study combining results from multiple clinical trials.[74,75] Transitions from "Post-Cystectomy" to "Metastatic Disease" were obtained from a large retrospective analysis in 888 patients,[76],[76] while transitions from "Post-Cystectomy" to "Death" were obtained from a retrospective study evaluating 678 patients.[77].[77] 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.[78].[78] The model inputs for these parameters are shown in Appendix Table E2.

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

Model Input	Nadofaragene Firadenovec	Oportuzumab Monatox	Pembrolizumab	Gemcitabine ± Docetaxel	Usual Care	Source
Probability of Complete Response at 3 months	53.4%	40.0%	40.6%	72.0%	0%	Boorjian 2020[73] Sesen Bio, data on file[40] Stuart 2019[69] Steinberg 2020[60]
Probability of Transitioning from Complete Response to NMIBC at 6 months	23.6%	20.0%	7.6%	16.7%	N/A	
Probability of Transitioning from Complete Response to NMIBC at 9 months	14.2%	31.3%	25.1%	14.7%	N/A	
Probability of Transitioning from Complete Response to NMIBC at 12 months	30.6%	9.1%	33.1%	6.3%	N/A	
Probability of Transitioning from Complete Response to NMIBC Each Cycle After 12 months	23.1%	15.4%	22.6%	2.6%	N/A	
Probability of Transitioning from NMIBC to MIBC Each Cycle	2.4%	2.4%	2.4%	2.4%	2.4%	

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

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

Model Input	Nadofaragene Firadenovec	Oportuzumab Monatox	Usual Care	Gemcitabine ± Docetaxel	Source
Probability of Complete Response at 3 months	72.9%	69.0%	0%	75.2%	Boorjian 2020[73] Sesen Bio, data on file[40] Stuart 2019[69]
Probability of Transitioning from Complete Response to NMIBC at 6 months	14.3%	14.5%	N/A	7.4%	
Probability of Transitioning from Complete Response to NMIBC at 9 months	6.7%	10.2%	N/A	14.9%	
Probability of Transitioning from Complete Response to NMIBC at 12 months	24.9%	5.7%	N/A	6.8%	
Probability of Transitioning from Complete Response to NMIBC Each Cycle After 12 Months	15.6%	8.5%	N/A	2.5%	
Probability of Transitioning from NMIBC to MIBC Each Cycle After 12 Months (Patients with HG Ta/T1)	3.4%	3.4%	3.4%	3.4%	

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," "Complete Response/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.

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," "Complete Response/Disease Free," "Persistent/Recurrent NMIBC," and "MIBC" were obtained from a study evaluating the EQ-5D in 472 patients with NMIBC.[79] The utility for "Metastatic Disease" was obtained from a study of 270 patients enrolled in the KEYNOTE-045 trial with metastatic urothelial carcinoma.[80] The "Post-Cystectomy" utility value was obtained from a decision model report, where utility was estimated from 25 urologists using the standard gamble method.[81] 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," "Complete Response/Disease Free," "Persistent/Recurrent NMIBC," and "MIBC" were obtained from a study evaluating the EQ-5D in 472 patients with NMIBC.[79] The utility for "Metastatic Disease" was obtained from a study of 270 patients enrolled in the KEYNOTE-045 trial with metastatic urothelial carcinoma.[80] The "Post-Cystectomy" utility value was obtained from a decision model report, where utility was estimated from 25 urologists using the standard gamble method.[81]

The above utility values 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. Perhaps for these reasons, 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	0.88	Patients with NMIBC	EQ-5D	Cox 2019[79]Cox 2019[79]
Disease Free	0.87	Patients with NMIBC	EQ-5D	Cox 2019[79]Cox 2019[79]
NMIBC	0.76	Patients with NMIBC	EQ-5D	Cox 2019[79]Cox 2019[79]
MIBC	0.75	Patients with NMIBC	EQ-5D	Cox 2019[79]Cox 2019[79]
Metastatic Disease	0.70	Patients enrolled in KEYNOTE-045 with metastatic urothelial carcinoma	EQ-5D	Slater 2020[80]
Post-Cystectomy	0.745	Non-patient urologists	Standard Gamble	Kulkarni 2012[81]

NMIBC: non-muscle invasive bladder cancer

Adverse Events

All AEs occurring in at least 5% of patients were included in the analysis. Since there were no treatment related AEs of grade 3 or 4 that reached a frequency of 5%, disutilities were not included in the model. However, urinary tract infection was a common AE with oportuzumab monatox, occurring with a frequency of 12%. Rash and pruritus were common adverse events with pembrolizumab, occurring at frequencies of 23% each. 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%). The cost for treating urinary tract infection, rash, and pruritus were factored into the model. Since urinary frequency, dysuria, and hematuria were unlikely to accrue significant cost or result in measurable long-term 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[82]
Rash, Pembrolizumab	23%	$95	0	CMS.gov[83] Redbook[84]
Pruritis, Pembrolizumab	23%	$95	0	CMS.gov[83] Redbook[84]

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.[36,40,85] 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 draft, the prices for nadofaragene firadenovec and oportuzumab monatox were not available. We therefore estimated the prices for nadofaragene firadenovec and oportuzumab monatox using the price of pembrolizumab. The price for pembrolizumab was derived using the US Department of Veteran Affairs Office of Procurement Federal Supply Schedule (FSS) prices. The price for gemcitabine ± docetaxel was estimated using WAC, obtained from Micromedex Red Book.[86] 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.	$3x10^{11}$ 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.	30 mg	$2,826**	$2,826**	$164,337**
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.	200 mg	$9,455*	$9,455*	$164,337
Gemcitabine ± docetaxel	Gemcitabine 1000 mg and docetaxel 37.5 mg administered 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

**For investigational drugs, the price for pembrolizumab was assumed in the model base-case.

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

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

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.[87] 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.[88] 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," "Complete Response/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.[88] The cost of "Metastatic Disease" was obtained from an abstract describing the first six months of therapy after the diagnosis of metastatic bladder cancer.[89] 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.[90,91] 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[88]
Disease Free	$1,211	Mossanen 2019[88]
NMIBC	$1,458	Mossanen 2019[88]
MIBC	$7,027	Mossanen 2019[88]
Cystectomy	$30,625 (one-time)	Leow 2014[90]
Post-Cystectomy	$8,665	Malangone-Monaco 2020[91]
Metastatic Disease	$24,905	Seal 2014[89]
Death	$500	Mossanen 2019[88]

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.[82] 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.[87]

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.[92] 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.[93] 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.[93] 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[81] and metastatic disease[80] were obtained from different sources than those for all other utilities[79] 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[81] and metastatic disease[80] were obtained from different sources than those for all other utilities[79] 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

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 usual care. 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 and oportuzumab monatox were not available at the time of publishing this draft document, we used prices in the model that were based on the annual price of pembrolizumab, taking into account differences in dosing frequency. 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 usual care 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 Usual Care 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)
Nadofaragene Firadenovec	$164,000*	$318,000	4.82	4.86	6.31	3.36
Oportuzumab Monatox	$164,000*	$307,000	4.80	4.84	6.28	3.33
Pembrolizumab	$164,000	$273,000	4.74	4.78	6.22	3.26
Gemcitabine ± Docetaxel	$440	$174,000	7.05	7.20	8.75	6.23
Usual Care	$0	$189,000	4.41	4.41	5.87	2.86

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

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

Table 5.11. Results for the Base Case for Nadofaragene Firadenovec and Oportuzumab Monatox Compared to Usual Care 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)
Nadofaragene Firadenovec	$164,000*	$319,000	5.08	5.17	6.56	3.60
Oportuzumab Monatox	$164,000*	$306,000	5.53	5.66	7.06	4.17
Gemcitabine ± Docetaxel	$440	$174,000	7.40	7.55	9.11	6.62
Usual Care	$0	$190,000	4.25	4.25	5.66	2.58

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

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

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 usual care (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). Note again that prices entered for nadofaragene firadenovec and oportuzumab monatox were based on the annual price of pembrolizumab.

Table 5.12. Incremental Cost-Effectiveness Ratios for Nadofaragene Firadenovec and Oportuzumab Monatox Compared to Pembrolizumab and Usual Care 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
Nadofaragene Firadenovec*	Usual Care	$317,000	$284,000	$291,000	$257,000
Oportuzumab Monatox*	Usual Care	$308,000	$276,000	$283,000	$248,000
Pembrolizumab	Usual Care	$257,000	$230,000	$236,000	$208,000
Gemcitabine ± Docetaxel	Usual Care	Dominates	Dominates	Dominates	Dominates

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

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

Table 5.13. Incremental Cost-Effectiveness Ratios for Nadofaragene Firadenovec and Oportuzumab Monatox Compared to Usual Care 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
Nadofaragene Firadenovec*	Usual Care	$156,000	$140,000	$142,000	$126,000
Oportuzumab Monatox*	Usual Care	$90,000	$82,000	$82,000	$72,000
Gemcitabine ± Docetaxel	Usual Care	Dominates	Dominates	Dominates	Dominates

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

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

In a sensitivity analysis, we varied the effectiveness of usual care from a 0% complete response, used in the base-case, to up to 60% in patients with HG Ta/T1. As the effectiveness of usual care 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 5.14 and 5.15.

Table 5.14. Impact of Varying the Effectiveness of Usual Care on the Incremental Cost-Effectiveness Ratios for Nadofaragene Firadenovec and Oportuzumab Monatox Compared to Usual Care in Patients with CIS ± Ta/T1

Effectiveness of Usual Care (% with Complete Response)	Nadofaragene Firadenovec* Cost per QALY Gained	Oportuzumab Monatox* Cost per QALY Gained
0% (Base Case)	$317,000	$308,000
10%	$336,000	$328,000
20%	$404,000	$400,000
30%	$652,000	$683,000

QALY: quality-adjusted life year

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

Table 5.15. Impact of Varying the Effectiveness of Usual Care on the Incremental Cost-Effectiveness Ratios for Nadofaragene Firadenovec and Oportuzumab Monatox Compared to Usual Care in Patients with High Grade Ta/T1

Effectiveness of Usual Care (% with Complete Response)	Nadofaragene Firadenovec* Cost per QALY Gained	Oportuzumab Monatox* Cost per QALY Gained
0% (Base Case)	$156,000	$90,000
10%	$160,000	$92,000
20%	$171,000	$96,000
30%	$192,000	$103,000
40%	$230,000	$115,000
50%	$307,000	$134,000
60%	$509,000	$166,000

QALY: quality-adjusted life year

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

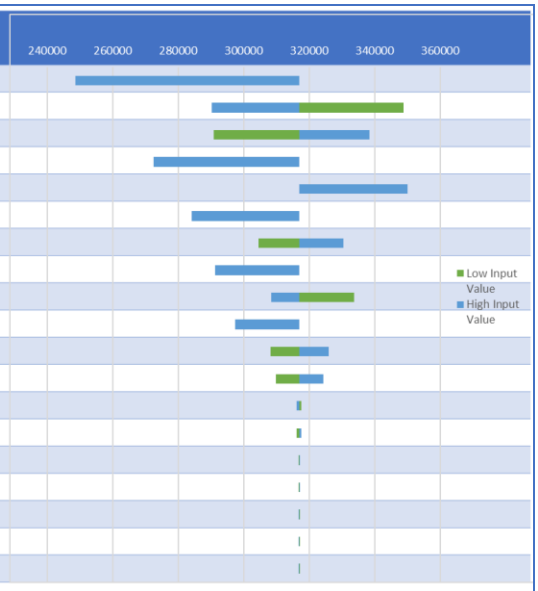
Sensitivity Analysis Results

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 usual care in both subgroups. The primary drivers of model uncertainty for patients with CIS ± Ta/T1 were the probabilities of CR (treatments and usual care) and of recurrence, especially after 12 months. Cost inputs had minimal impact on the cost-effectiveness results. The utility of being in CR/disease-free and that for persistent/recurrent NMIBC had the largest impact on the model results. For patients with HG Ta/T1 disease, the probability of recurrence was the most impactful, followed by the probability of CR with treatment. Costs and utilities had a similar impact on the model in the HG Ta/T1 subgroup as with the CIS ± Ta/T1 subgroup. 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 Usual Care in Patients with CIS ± Ta/T1

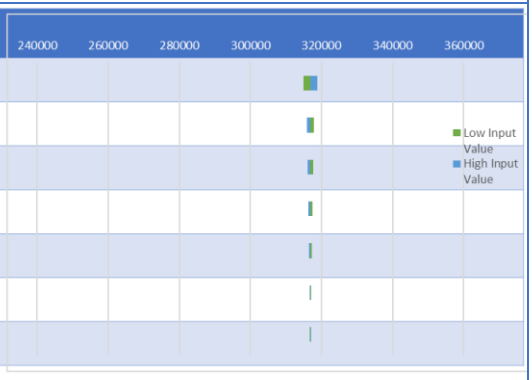
Probabilities

Probability	Low Input Value	High Input Value
Disease-free to MIBC at 6 months, Nadofaragene firadenovec	0	0.05
Complete Response, Nadofaragene firadenovec	0.4858	0.5822
Recurrence after 12 months, Nadofaragene firadenovec	0.1901	0.2716
Disease-free to MIBC at 6 months, Nadofaragene firadenovec	0	0.05
Complete Response, Usual Care	0	0.05
Disease-free to MIBC at 6 months, Nadofaragene firadenovec	0	0.05
Recurrence at 6 months, Nadofaragene firadenovec	0.1949	0.277
Disease-free to MIBC at 9 months, Nadofaragene firadenovec	0	0.05
Progression to MIBC, All Treatments	0	0.0480
Progression to Metastatic Disease, All Treatments	0	0.05
Recurrence at 12 months, Nadofaragene firadenovec	0.2612	0.3502
Recurrence at 9 months, Nadofaragene firadenovec	0.1084	0.1759
NMIBC Cystectomy, All Treatments	0.0495	0.0525
Post-Cystectomy to Metastatic Disease, All Treatments	0.0491	0.0646
MIBC Cystectomy, All Treatments	0.4912	0.5088
MIBC to Metatstatic Disease, All Treatments	0.0328	0.0452
Post-Cystectomy Mortality, All Treatments	0.0326	0.0477
Metastatic Disease Mortality, All Treatments	0.1167	0.1505
MIBC Mortality, All Treatments	0.0336	0.0461



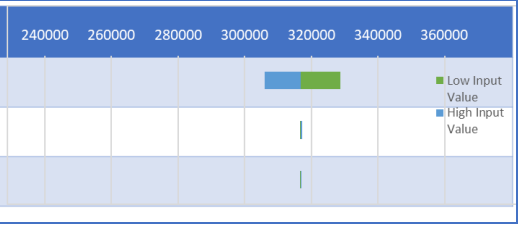
Costs

Costs	Low Input Value	High Input Value
Complete Response/ Disease-free	908.21	1513.68
Metastatic disease	18678.90	31131.5
Post-Cystectomy	6498.41	10830.7
Cystectomy	22969	38281.7
Persistent/ Recurrent NMIBC	1093.39	1822.32
MIBC	5269.97	8783.29
Transition to Death State	374.70	624.50



Utilities

Utilities	Low Input Value	High Input Value
Complete Response/ Disease-free	0.8467	0.8933
Persistent/ Recurrent NMIBC	0.7066	0.8134
MIBC	0.6682	0.8318

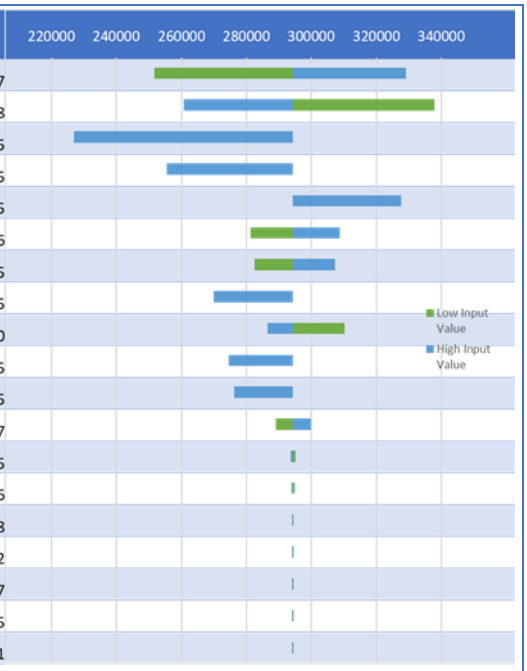


*Price for nadofaragene firadenovec and oportuzumab monatox was based on annual price of pembrolizumab

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

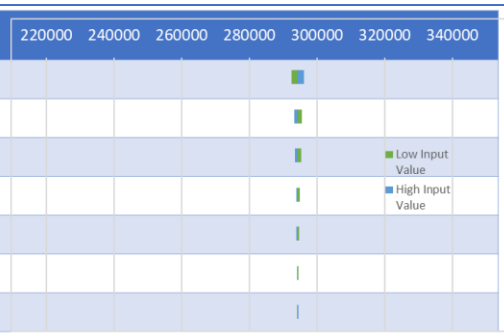
Probabilities

Probability	Low Input Value	High Input Value
Recurrence after 12 months, Nadofaragene firadenovec	0.1168	0.1917
Complete Response, Nadofaragene firadenovec	0.3492	0.4508
Disease-free to MIBC at 6 months, Oportuzumab monatox	0	0.05
Disease-free to MIBC at 6 months, Oportuzumab monatox	0	0.05
Complete Response, Usual Care	0	0.05
Recurrence at 9 months, Nadofaragene firadenovec	0.2644	0.3606
Recurrence at 6 months, Nadofaragene firadenovec	0.1585	0.2415
Disease-free to MIBC at 6 months, Oportuzumab monatox	0	0.05
Progression to MIBC, All Treatments	0	0.0480
Disease-free to MIBC at 9 months, Oportuzumab monatox	0	0.05
Progression to Metastatic Disease, All Treatments	0	0.05
Recurrence at 12 months, Nadofaragene firadenovec	0.0611	0.1207
NMIBC Cystectomy, All Treatments	0.0495	0.0525
Post-Cystectomy to Metastatic Disease, All Treatments	0.0491	0.0646
MIBC Cystectomy, All Treatments	0.4912	0.5088
MIBC to Metastatic Disease, All Treatments	0.0328	0.0452
Post-Cystectomy Mortality, All Treatments	0.0326	0.0477
Metastatic Disease Mortality, All Treatments	0.1167	0.1505
MIBC Mortality, All Treatments	0.0336	0.0461



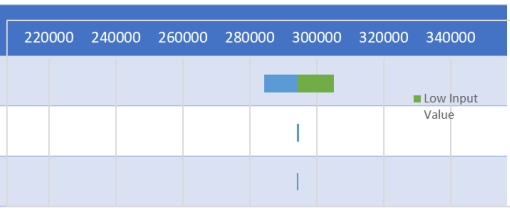
Costs

Costs	Low Input Value	High Input Value
Complete Response/ Disease-free	908.21	1513.68
Metastatic disease	18678.88	31131.46
Post-Cystectomy	6498.41	10830.68
Cystectomy	22969.04	38281.73
Persistent/ Recurrent NMIBC	1093.39	1822.32
MIBC	5269.97	8783.29
Transition to Death State	374.70	624.50



Utilities

Utilities	Low Input Value	High Input Value
Complete Response/ Disease-free	0.8467	0.8933
Persistent/ Recurrent NMIBC	0.7066	0.8134
MIBC	0.6682	0.8318



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

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

Probabilities

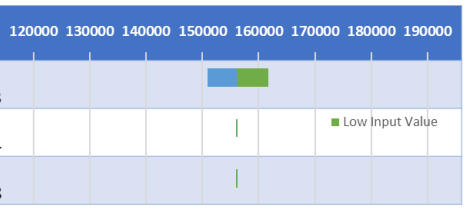
Probability	Low Input Value	High Input Value
Recurrence after 12 months, Nadofaragene firadenovec	0.1048	0.2075
Complete Response, Nadofaragene firadenovec	0.6661	0.7919
Disease-free to MIBC after 9 months, Nadofaragene firadenovec	0	0.05
Recurrence at 6 months, Nadofaragene firadenovec	0.0932	0.1921
Recurrence at 12 months, Nadofaragene firadenovec	0.1876	0.3098
Complete Response, Usual Care	0	0.05
Progression to MIBC, All Treatments	0.0055	0.0631
Recurrence at 9 months, Nadofaragene firadenovec	0.0318	0.1026
Progression to Metastatic Disease, All Treatments	0	0.05
Disease-free to MIBC at 6 months, Nadofaragene firadenovec	0	0.05
Disease-free to MIBC at 9 months, Nadofaragene firadenovec	0	0.05
Disease-free to Metastatic Disease, Nadofaragene firadenovec	0	0.05
NMIBC Cystectomy, All Treatments	0.0495	0.0525
Post-Cystectomy to Metastatic Disease, All Treatments	0.0491	0.0646
MIBC Cystectomy, All Treatments	0.4912	0.5088
MIBC to Metastatic Disease, All Treatments	0.0328	0.0452
Post-Cystectomy Mortality, All Treatments	0.0326	0.0477
Metastatic Disease Mortality, All Treatments	0.1167	0.1505
MIBC Mortality, All Treatments	0.0336	0.0461

Costs

Cost	Low Input Value	High Input Value
Complete Response/ Disease-free	908.21	1513.7
Metastatic disease	18679	31131
Post-Cystectomy	6498.4	10831
Cystectomy	22969	38282
Persistent/ Recurrent NMIBC	1093.4	1822.3
MIBC	5270	8783.3
Transition to Death State	374.7	624.5

Utilities

Utilities	Low Input Value	High Input Value
Complete Response/ Disease-free	0.8467	0.8933
Persistent/ Recurrent NMIBC	0.7066	0.8134
MIBC	0.6682	0.8318

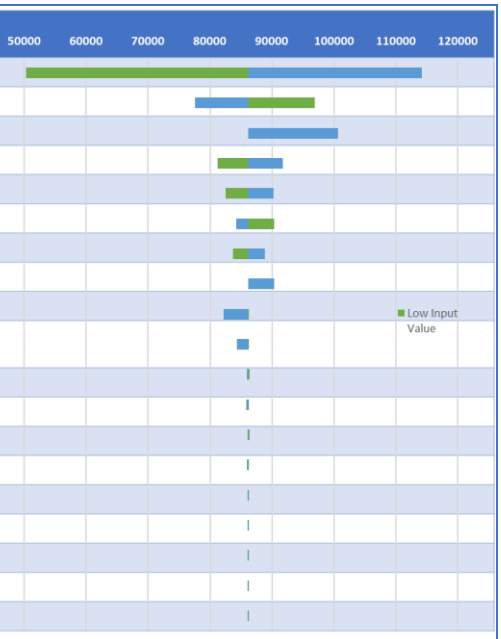


*Price for nadofaragene firadenovec and oportuzumab monatox was based on annual price of pembrolizumab

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

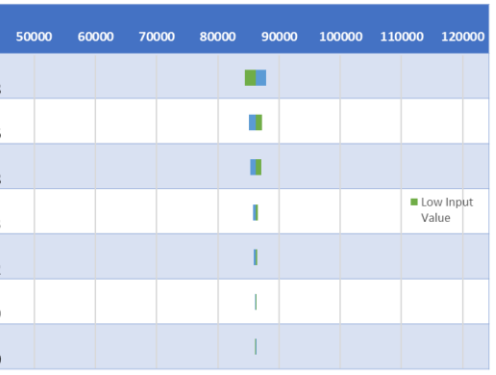
Probabilities

Probability	Low Input Value	High Input Value
Recurrence after 12 months, Oportuzumab monatox	0.04104	0.1293
Complete Response, Oportuzumab monatox	0.6169	0.7631
Disease-free to Metastatic Disease, Oportuzumab monatox	0	0.05
Recurrence at 6 months, Oportuzumab monatox	0.0893	0.2006
Recurrence at 9 months, Oportuzumab monatox	0.0539	0.1495
Progression to MIBC, All Treatments	0.0055	0.0631
Recurrence at 12 months, Oportuzumab monatox	0.0201	0.0931
Complete Response, Usual Care	0	0.05
Progression to Metastatic Disease, All Treatments	0	0.05
Disease-free to MIBC after 9 months, Oportuzumab monatox	0	0.05
Post-Cystectomy to Metastatic Disease, All Treatments	0.0491	0.0646
Disease-free to MIBC at 6 months, Oportuzumab monatox	0	0.05
NMIBC Cystectomy, All Treatments	0.0495	0.0525
Disease-free to MIBC at 9 months, Oportuzumab monatox	0	0.05
MIBC to Metastatic Disease, All Treatments	0.0328	0.0452
Post-Cystectomy Mortality, All Treatments	0.0326	0.0477
Metastatic Disease Mortality, All Treatments	0.1167	0.1505
MIBC Cystectomy, All Treatments	0.4912	0.5088
MIBC Mortality, All Treatments	0.0336	0.0461



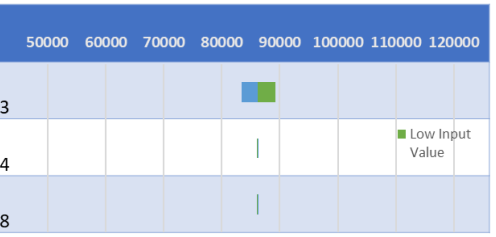
Costs

Cost	Low Input Value	High Input Value
Complete Response/ Disease-free	908.21	1513.68
Metastatic disease	18678.88	31131.46
Post-Cystectomy	6498.41	10830.68
Cystectomy	22969.04	38281.73
Persistent/ Recurrent NMIBC	1093.40	1822.32
MIBC	5269.972	8783.29
Transition to Death State	374.70	624.50



Utilities

Utility	Low Input Value	High Input Value
Complete Response/ Disease-free	0.8467	0.8933
Persistent/ Recurrent NMIBC	0.7066	0.8134
MIBC	0.6682	0.8318



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

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

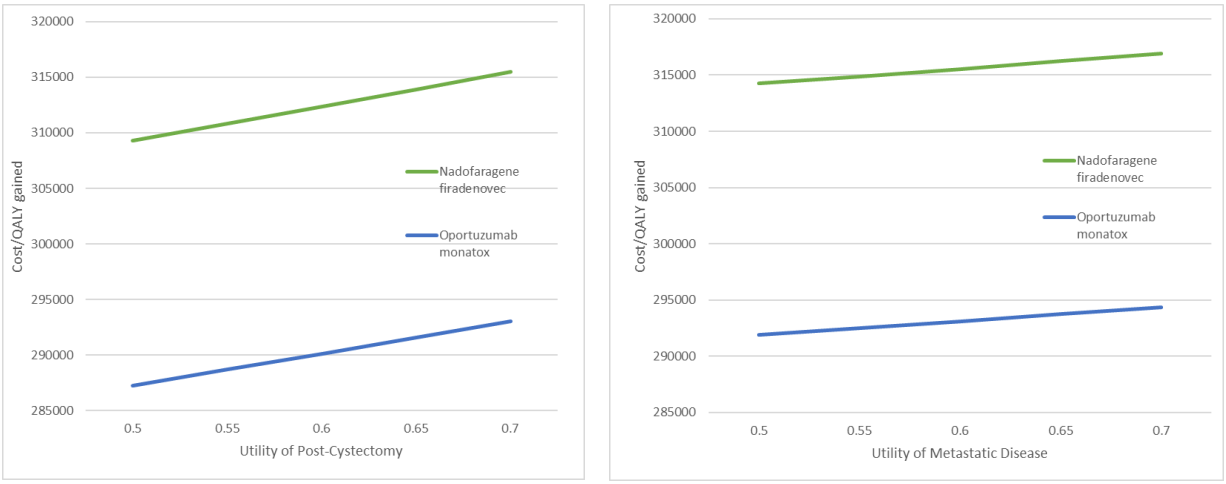
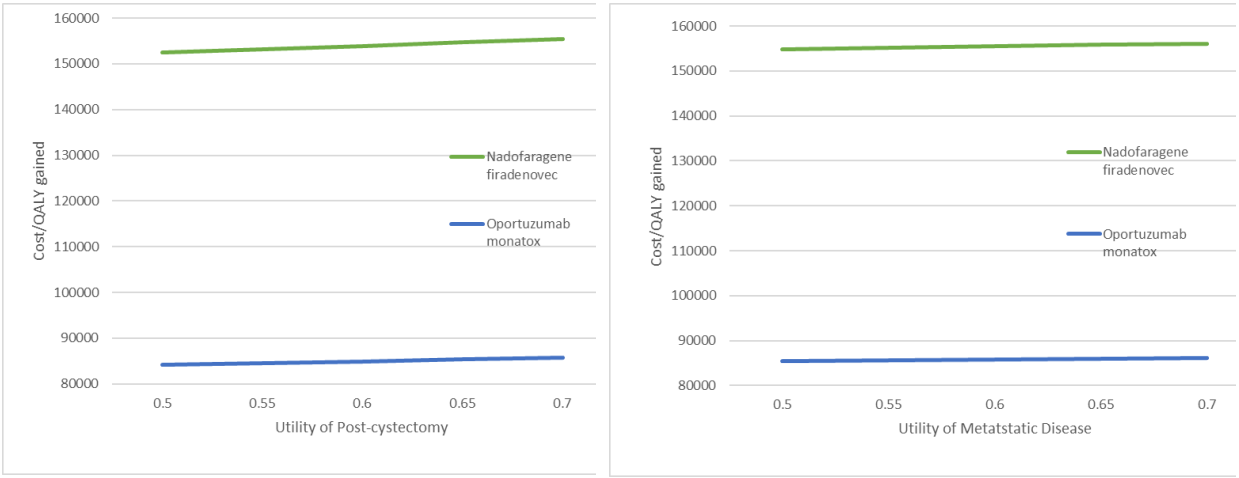


Figure 5.7. One-Way Sensitivity Analysis Varying Utility of Post-Cystectomy and Metastatic Disease in Patients with HG Ta/T1



Altering the probability of patients with MIBC undergoing cystectomy, from the base-case value of 50% per cycle, to 0% to 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 each other and with pembrolizumab and

usual care for the CIS ± Ta/T1 subgroup and with usual care only for the HG Ta/T1 subgroup. At lower thresholds of $50,000, $100,000, and $150,000 per QALY gained, nadofaragene firadenovec and oportuzumab monatox were rarely cost effective in the CIS ± Ta/T1 subgroup (0% and 2%, respectively) and in the HG Ta/T1 subgroup (6% and 20%, respectively). The full results are shown in Tables 5.16 and 5.17.

Table 5.16. Probabilistic Sensitivity Analysis Results: Nadofaragene Firadenovec and Oportuzumab Monatox Compared to Pembrolizumab and Usual Care 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%	0%	0%	0%	6%
Oportuzumab Monatox	0%	0%	0%	4%	23%

QALY: quality-adjusted life year

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

Table 5.17. Probabilistic Sensitivity Analysis Results: Nadofaragene Firadenovec and Oportuzumab Monatox Compared to Usual Care 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	0%	4%	46%	91%	100%
Oportuzumab Monatox	14%	69%	95%	100%	100%

QALY: quality-adjusted life year

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

Scenario Analyses Results

Threshold Analyses Results

Tables 5.18 and 5.19 show the price per instillation required to meet cost-effectiveness thresholds of $50,000, $100,000, and $150,000 per QALY gained. Note that these results are preliminary and, for reasons discussed in Section 7, should not be assumed to reflect the health-benefit price benchmarks that will be provided in the next version of this report.

Table 5.18. Threshold Analysis Results in Patients with CIS ± Ta/T1

	WAC per Unit	Net Price per Unit	Unit Price to Achieve $50,000 per QALY	Unit Price to Achieve $100,000 per QALY	Unit Price to Achieve $150,000 per QALY
Nadofaragene Firadenovec	N/A	N/A	$6,900	$13,300	$19,700
Oportuzumab Monatox	N/A	N/A	$420	$890	$1,350

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

Table 5.19. Threshold Analysis Results in Patients with High Grade Ta/T1

	WAC per Unit	Net Price per Unit	Unit Price to Achieve $50,000 per QALY	Unit Price to Achieve $100,000 per QALY	Unit Price to Achieve $150,000 per QALY
Nadofaragene Firadenovec	N/A	N/A	$13,800	$26,700	$39,500
Oportuzumab Monatox	N/A	N/A	$1,580	$3,100	$4,700

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,[94,95] surveillance,[88,96,97] non-drug treatment,[94,95] surveillance,[88,96,97] non-drug treatment,[98-100,81,101,102] and drug treatment.[98-100] All of the studies utilized a Markov or semi-Markov model, except for one evaluating a diagnostic approach,[95],[95] 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.[81,99]

Cycle lengths in these analyses varied from three months to one year. Time horizons varied between two years[96] and lifetime.[81,97] Of those studies evaluating drug treatments, one study evaluated pembrolizumab as second-line treatment of advanced bladder cancer, a different population;[98] one study evaluated low-dose BCG in patients with intermediate and high-risk NMIBC;[100] and one study evaluated radical cystectomy compared with mitomycin in BCG-refractory patients.[99] Two studies evaluated BCG-refractory high-risk populations similar to ours, one comparing cystectomy to no cystectomy[81] and one evaluating radical cystectomy compared with mitomycin.[99] Cycle lengths in these analyses varied from three months to one year. Time horizons varied between two years[96] and lifetime.[81,97] Of those studies evaluating drug treatments, one study evaluated pembrolizumab as second-line treatment of advanced bladder cancer, a different population;[98] one study evaluated low-dose BCG in patients with intermediate and high-risk NMIBC;[100] and one study evaluated radical cystectomy compared with mitomycin in BCG-refractory patients.[99] Two studies evaluated BCG-refractory high-risk populations similar to ours, one comparing cystectomy to no cystectomy[81] and one evaluating radical cystectomy compared with mitomycin.[99]

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.[88,94,97] One of the models was particularly helpful in providing cost inputs for our model.[88] 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.[81]

One of the models reviewed potentially competing treatments for nadofaragene firadenovec and oportuzumab monatox in a similar population.[99] 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 utility of these treatments were not considered in this model. By comparison, the five-year mortality and five-year costs in our model were 36% and approximately $91,000 (excluding treatment costs), respectively, for the CIS ± Ta/T1 subgroup and 30% and approximately $81,000 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 usual care 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.

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 poorer treatment outcomes and lower drug costs. The cost effectiveness of longer treatment durations could not be modeled because of unknown impact of longer durations on high-grade recurrence free survival and progression-free survival.

Another important uncertainty is the long-term effect of pembrolizumab, a systemic treatment, on outcomes such as progression to metastatic disease. Given that there is very limited data on progression to metastatic disease after receiving pembrolizumab, we modeled no additional benefit with pembrolizumab. Instead, we modeled progression from NMIBC to MIBC using the average

outcomes of nadofaragene firadenovec and oportuzumab monatox and from MIBC to metastatic disease using results from Griffiths et al.[75]

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, 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, 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 are 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

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 considered cost effective. Using a preliminary input price, equal to that of the annual price of pembrolizumab and an effectiveness for the comparator of 0% (i.e., 0% of patients achieve complete response), resulted in cost-effectiveness ratios ranging from well below $150,000 per QALY gained (for patients with HG Ta/T1 receiving oportuzumab monatox) to well over $150,000 per QALY gained (for patients with CIS ± Ta/T1 with either treatment). The resulting threshold price for nadofaragene firadenovec in the HG Ta/T1 subgroup was roughly double that of the price in the CIS ± Ta/T1 subgroup. The difference was even more pronounced for oportuzumab monatox, where the threshold price was nearly four times as high.

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, but at a relatively high cost. In addition, the QALY gains appeared to be smaller than those seen with any of the other treatments. However, caution should be used when making these comparisons, as data comes from uncontrolled trials. Additionally, long-term outcomes of a systemic treatment such as pembrolizumab are not known and may change these results. Sensitivity analyses demonstrated that progression-free survival was one of the more important factors in determining the incremental cost effectiveness of treatments.

Gemcitabine ± docetaxel was more effective and less costly, resulting in it dominating usual care. Although direct comparison with nadofaragene firadenovec and oportuzumab monatox is difficult given the differences in study designs and lack of comparators, gemcitabine ± docetaxel appears to be a cost-effective option for patients with BCG-unresponsive NMIBC who can tolerate an intravesical chemotherapy.

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,[103] 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.[104,105] 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.[106] 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.[107,108] 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 6.0 QALYs, with a proportional shortfall of 0.56, representing a loss of 56% 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.[105]

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

	From ICER Reports			From iDBC tool[109]	
Condition	**Age**	**% Male**	**Total Undiscounted QALYs with Standard of Care**	**Absolute Shortfall**	**Proportional Shortfall**
BCG-Unresponsive High-Risk NMIBC	72	80	4.64	6.0	0.56
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

ICER does not provide health benefit price benchmarks as part of draft reports because results may change with revision following receipt of public comments. We therefore caution readers against assuming that the values provided in the Threshold Analyses Results section of this draft report will match the health-benefit price benchmarks that will be presented in the next version of this report.

8. Potential Budget Impact

8.1 Overview

Note that these results are preliminary and, for reasons discussed in Section 7, should not be assumed to reflect the health-benefit price benchmarks that will be provided in the next version of this report.

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 the three 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.[12] We assumed that T1 and CIS are considered high-grade disease while 10% of Ta cancers are considered high grade.[27] For the proportion of patients who are BCG-unresponsive/refractory, we assumed that approximately 38% will be classified as BCG non-responders.[110] 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 (i.e., no specific bladder cancer-related treatment).

ICER's methods for estimating potential budget impact are described in detail elsewhere[111] 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 usual care, based on the assumed placeholder price of $164,337 per one year of treatment. The average potential budgetary impact for nadofaragene firadenovec was an additional per-patient cost of approximately $128,000 in year one, with net savings in following years leading to a decline in cumulative costs to approximately $110,000 by year five. The average potential budgetary impact for oportuzumab monatox followed a similar pattern, with an additional per-patient cost of approximately $112,000 in year one and net savings in following years leading to a decline in cumulative costs to approximately $88,000 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

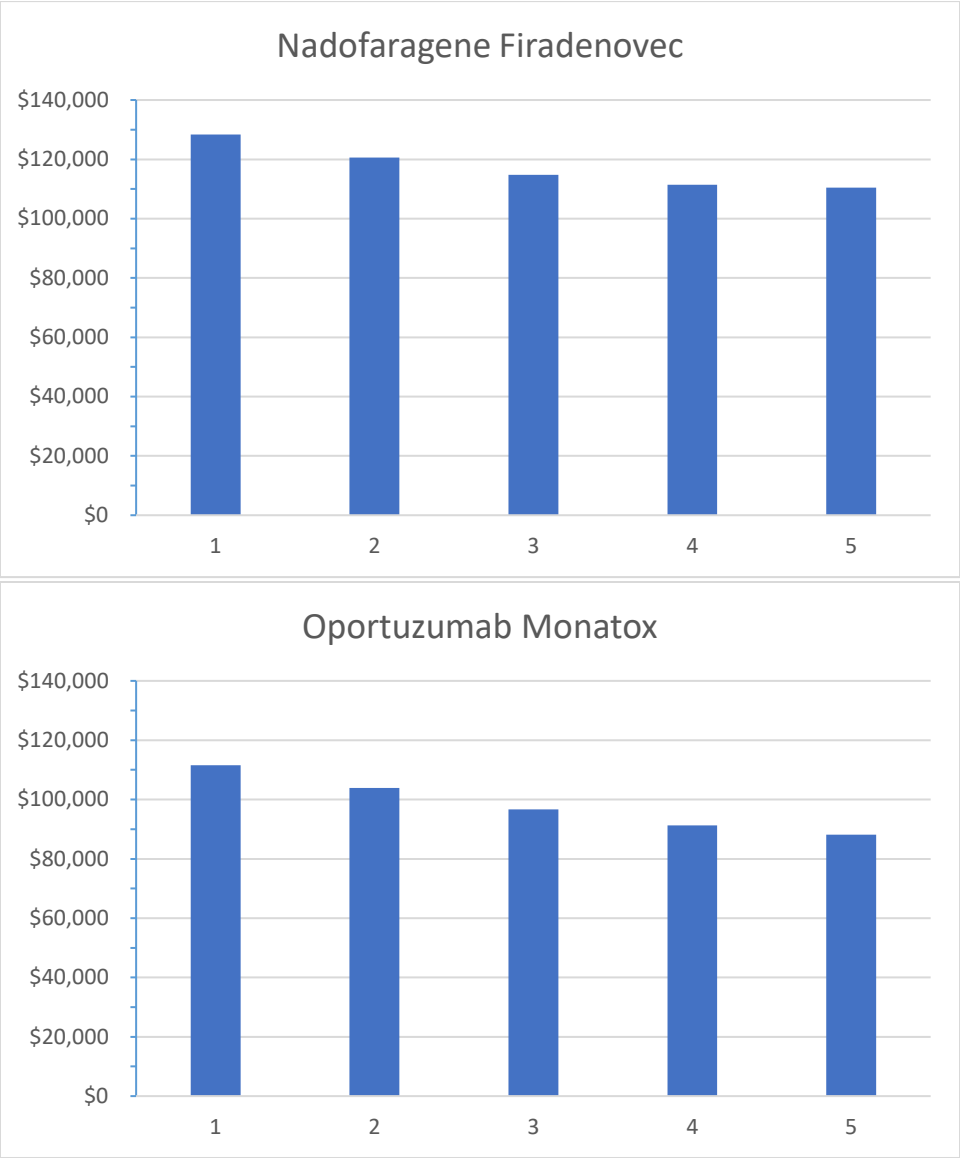


Figure 8.2 illustrates the potential budget impact of nadofaragene firadenovec treatment of the eligible population, based on the assumed placeholder price ($164,337 per year of treatment), and the weighted-average prices to reach $150,000, $100,000, and $50,000 per QALY ($78,812, $53,180, and $27,552 per year of treatment, respectively) compared to usual care. As shown in Figure 8.2, approximately 50% 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 62% of patients could be treated in a given year without crossing the budget impact threshold at the $150,000 per QALY threshold price, while almost all (98%) 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 41% of the potential budget impact threshold.

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

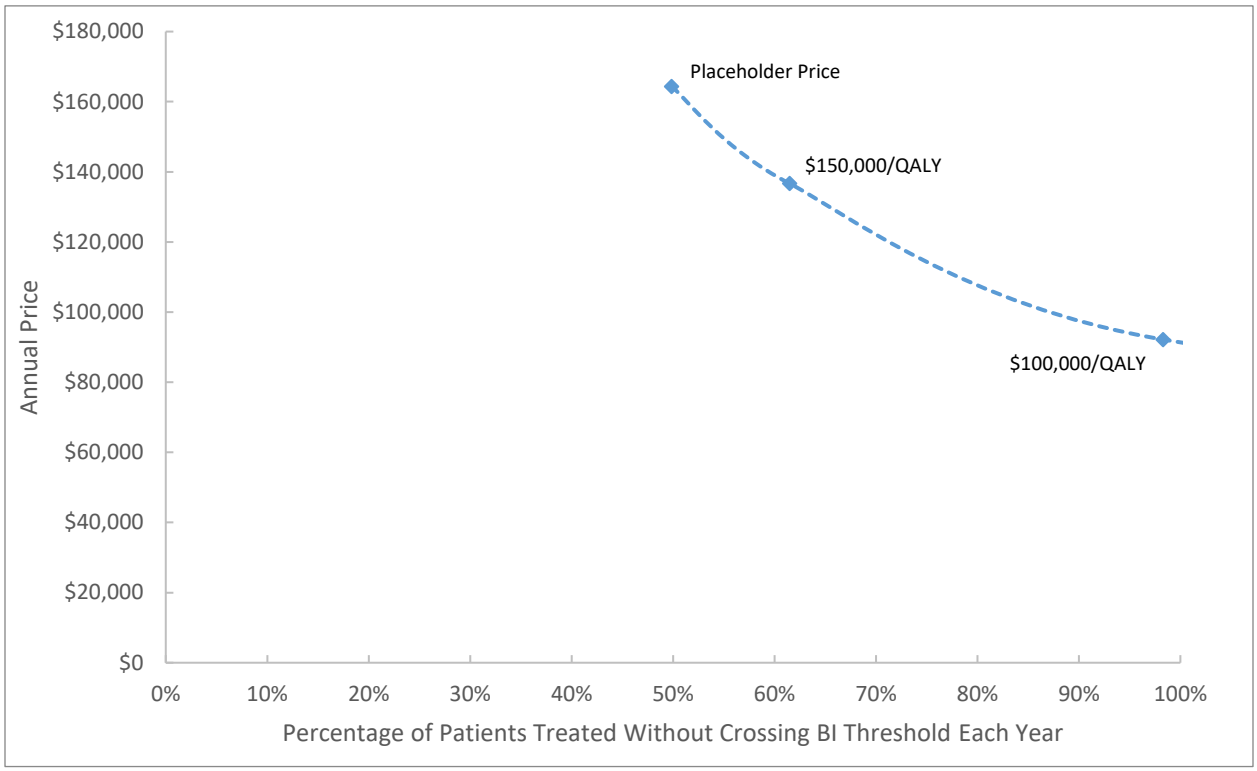
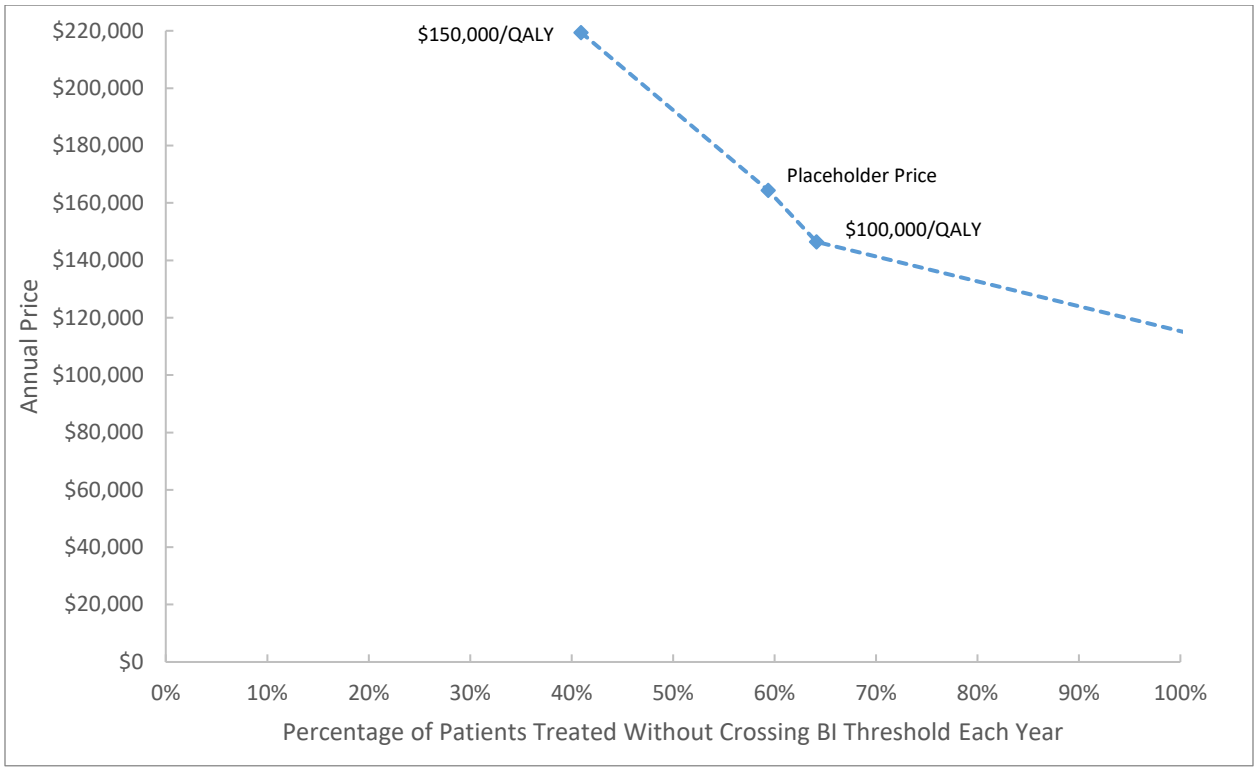


Figure 8.3 illustrates the potential budget impact of oportuzumab monatox treatment of the eligible population, based on the assumed placeholder price ($164,337 per year), and the weighted-average prices to reach $150,000, $100,000, and $50,000 per QALY ($196,241, $131,012, and $65,822 per year of treatment, respectively) compared to usual care. As shown in Figure 8.3, approximately 59% 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 41% 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 64% 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 68% of the threshold.

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



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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).

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., healthcare 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[31]

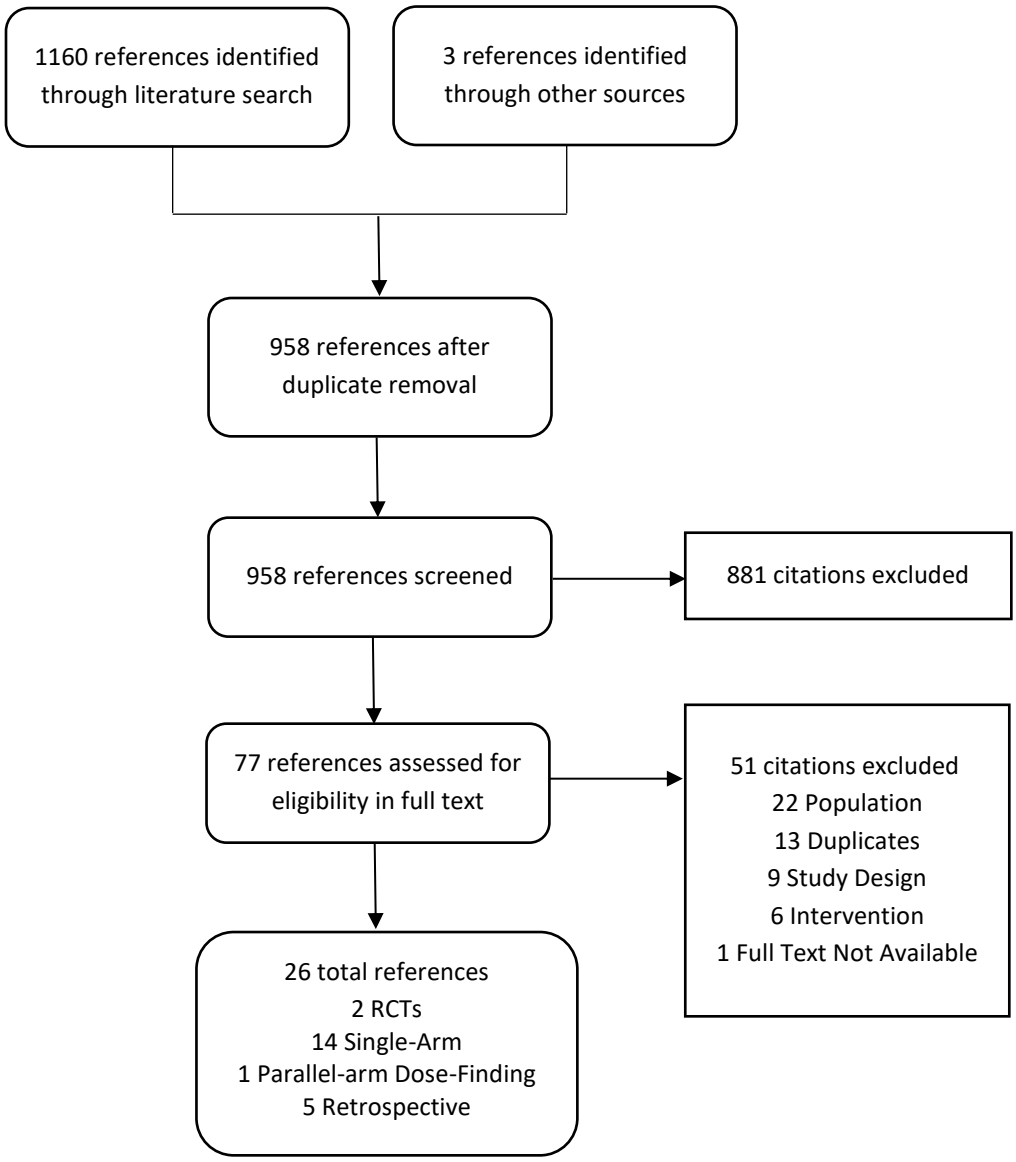
Table A2. Search Strategy of Ovid MEDLINE® Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE® Daily, Ovid MEDLINE and Versions® 1946 to Present

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

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

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.

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

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 within 6 months of the last dose of	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

			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) • Concurrent extra-vesical non-muscle invasive TCC of the urothelium	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

			• 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 • Known human immunodeficiency virus (HIV) or active Hepatitis B or C infection • Received a live virus vaccine within 30 days; 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	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

Bladder Cancer (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.

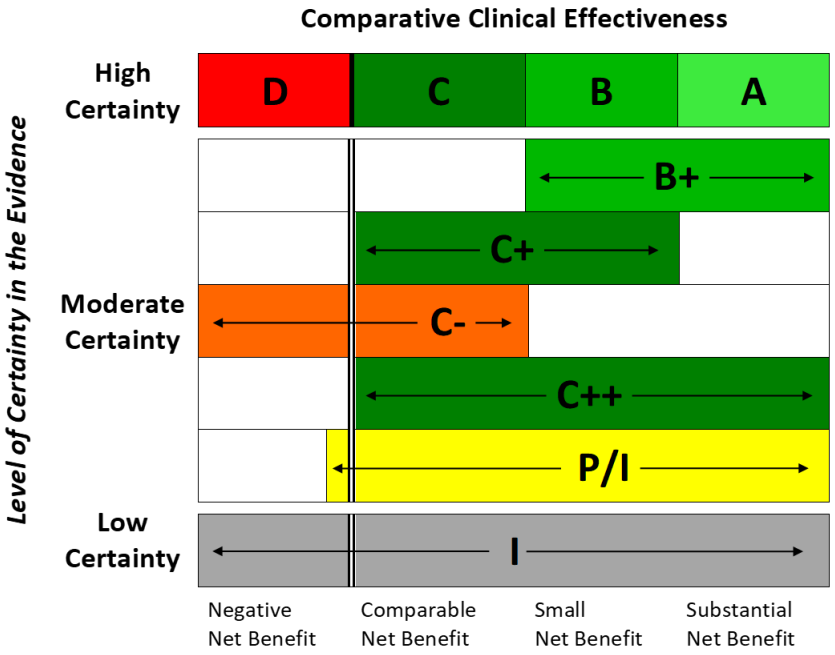
ICER Evidence Rating

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.[32,112]

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 (but nonzero) 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[33] 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 presence of hydronephrosis secondary to primary tumor

Phase II SUO-CTC[34] 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

Phase I **Dinney 2013[35]** 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[37] 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 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**[38] NCT00462488 Sponsor: Viventia Bio (Sesen Bio) Completion Date: Oct 2009	Open-Label, multicenter, 2-arm trial with a single stage design Multicenter: 21 sites in North America (Mar 2007-July 2008) • 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	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 Maintenance dosing regimens varies between cohorts - see full text for diagram)	**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 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**[39] 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 • Patients assessed at week 12	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 reached; therefore, an additional escalation through 13.73, 17.85, 23.20, and 30.16 mg was undertaken.	**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** • 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				
Phase II KEYNOTE 057[42,43] 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				
Addeo 2010[55] 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[47] 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[48] 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 thereafter • Lost to follow-up: n=1	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

				Exclusions • **Histologically confirmed carcinoma in situ** • Previous partial cystectomy, prior pelvic irradiation and clinical evidence of other malignancies
Perdona 2010[49] 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 tomograpy-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[50] 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 treatments) • Cystoscopy, cytology, and biopsy performed at 3 months and then cystoscopy and cytology	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 recurrence (appearance of new lesions of any stage or grade) were removed	**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 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

	performed every 3 months up to month 12		from protocol treatment	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[51] 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[52] 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** • Prior radiation to the pelvis and intractable urinary tract infection

Di Lorenzo 2010[56] 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[113] Department of Urology, University of Florence Department of Urology, University of Florence	Non-randomized, prospective, Phase II Multicenter: 5 urology departments in Tuscany, Italy • 6 month enrollment period • 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.	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 (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

	Ultrasonography of the urinary tract required every 6 months • Loss to follow-up: n=2			
Fiorito 2014[54] 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[57]	Retrospective chart review between Jan 1999 and Oct 2011 • 3-week treatment period separated by weeks of rest for a total of 12 instillations	Patients with NMIBC tumors with BCG failure N=69	Two courses of 2000 mg gemcitabine twice weekly for 3 weeks with courses separated by a week of rest for a total of 12 instillations	**Inclusions** • Patients with NMIBC tumors who were treated with intravesical gemcitabine after failure of BCG treatment **Exclusions** • NR

Gemcitabine with Docetaxel				
Steinberg 2020[114] 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)

Daniels 2020[61]	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[63] 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 if disease free beyond 2 years	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

Milbar 2017[62]	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

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[33]	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)
Phase II SUO-CTC[34]	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[35]	rAd-IFN $3x10^{9}$ to $3x10^{11}$ vps/mL	17	No overall presented - only individual patient-level data												
Oportuzumab Monatox															
Phase III VISTA[37,40]	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[38]	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[39]	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[42,43]	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[55]	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[47]	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[48]	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[49]	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[50]	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[51]	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)
Dalbagni 2006[52]	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[56]	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):	NR	NR	NR	NR	18 (45)	22 (55)	NR	NR	NR	NR	13 (32)	27 (68)

			71.4 (7.9)												
Bartoletti 2005[113]	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[54]	Gemcitabine	41	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Sternberg 2013[57]	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[114]	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[61]	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[63]	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[62]	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)

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/ Populations	N	Complete Response, n (%)				High-Grade Recurrence Free Survival, n %					Median Time to Recurrence, Months	Disease Recurrence, n (%)	Disease Progression	Progression to ≥ MIBC
			months				*months*								
			3	6	9	12	3	6	9	12	24				
Nadofaragene Firadenovec															
Phase III[33,36]	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	[redacted]	[redacted]	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	[redacted]	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	[redacted]	8 (5.3)
Phase II SUO-CTC[34]	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[35]	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[37,40]	CIS ± Ta/T1 disease	93	36 (40)	25 (28)	19 (21)	15 (17)	NR (42)	NR (32)	NR (22)	NR (20)	NR (13)	287 Days (Range: 86-651)	NR	NR	NR

	Ta/T1 Papillary disease	40	NR	NR	NR	NR	NR (69)	NR (59)	NR (53)	NR (50)	NR (37)	402 Days	NR	NR	NR
	Overall	133	NR	NR	NR	NR	NR (50)	NR (40)	NR (31)	NR (29)	NR (21)	NR	NR	NR	NR
Phase II Kowalski 2012[38]	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[39]	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[42,43]	Overall: CIS ± Ta/T1 disease	96	39 (40.6)	NR	NR	NR (19)	NR	NR	NR	NR	NR	16.2 (0-30.4)	20 (47.6)	NR	0 (0)
Gemcitabine															
Addeo 2010[55]	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[47]	Gemcitabine	19	NR	NR	NR	NR	NR	NR	NR	8 (42)	NR	8 (2-62)	12 (63)	NR	NR
Gunelli 2007[48]	Gemcitabine	40	NR	38 (95)	NR	NR	NR	37 (95)*	NR	30 (82)*	14 (66)*	NR	14 (35)	NR	NR
Perdona 2010[49]	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[50]	Gemcitabine	47	19 (40)	NR	NR	NR	NR (54)*	NR (53)*	NR (30)*	13 (28)*	10 (21) *	6.1	40 (85)	17 (36)	NR
Dalbagni 2002[51]	Gemcitabine	18	Time point at 8 weeks: 7 (39)				NR	NR	NR	NR	NR	NR	NR	NR	NR
Dalbagni 2006[52]	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[56]	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[113]	Gemcitabine	40	NR	NR	NR	NR	NR	NR	NR	27 (68)	NR	NR	13 (32.5)	NR	NR
Fiorito 2014[54]	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[57]	Gemcitabine	69	27 (39)	NR	NR	NR	NR	NR	NR	NR	NR	NR	46 (67)	11 (16)	NR
Gemcitabine/Docetaxel															
Steinberg 2020[114]	Gem/Doc	276	NR	NR	NR	NR	NR	NR	(~79 %)	179 (65)	144 (52)	6.8	NR	21 (7.6)	11 (4)
Daniels 2020[61]	Gem/Doc	59	37 (71)	NR	NR	NR	NR	NR	NR	28 (53)	18 (35)	NR	16 (27)	NR	NR
Steinberg 2015[63]	Gem/Doc	45	NR	NR	NR	NR	30 (66)	NR	NR	24 (54)	15 (34)	5.9	NR	NR	NR
Milbar 2017[62]	BCG-Unresponsive /Relapsing Cohort	25	NR	NR	NR	NR	NR	NR	NR	12 (49)	9 (34)	6.5	15 (60)	NR	NR

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	Median Duration of Response
Nadofaragene Firadenovec							
Phase III[33,36]	***Complete Response Rate, n (%)***						
	Overall	90 (59.6)	72 (47.7)	64 (42.4)	46 (30.5)	NR	NR
	CIS ± Ta/T1	55 (53.4)	42 (40.8)	36 (35.0)	25 (24.3)	NR	NR
	High-grade Ta/T1 alone	35 (72.9)	30 (62.5)	28 (58.3)	21 (43.8)	NR	NR
	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	90 (59.6)	72 (47.7)	64 (42.4)	46 (30.5)	NR	NR
	CIS ± Ta/T1	55 (53.4)	42 (40.8)	36 (35.0)	25 (24.3)	NR	NR
	High-grade Ta/T1 alone	35 (72.9)	30 (62.5)	28 (58.3)	21 (43.8)	NR	NR
	1+ Prior BCG Cycles	NR	NR	NR	NR	NR	NR
	2+ Prior BCG Cycles	NR	NR	NR	NR	NR	NR
	Progression						
	Overall						NA
	CIS ± Ta/T1						NA
	High-grade Ta/T1 alone						NA
	1+ Prior BCG Cycles	NR	NR	NR	NR	NR	NA
	2+ Prior BCG Cycles	NR	NR	NR	NR	NR	NA
	Cystectomy						
	Overall						NA
	CIS ± Ta/T1						NA
	High-grade Ta/T1 alone						NA
	1+ Prior BCG Cycles	NR	NR	NR	NR	NR	NA
	2+ Prior BCG Cycles	NR	NR	NR	NR	NR	NA
Oportuzumab Monatox							
Phase III[40]	***Complete Response Rate, n (%), 95% CI***						

	Time Point: Months	3	6	9	12	24	Median Duration of Response
	Overall (n=133)	NR	NR	NR	NR	NR	NR
	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 (95% CIs 154.0 - N/E; range: 89-651 days)
	High-grade Ta/T1 alone (n=40)	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 (95% CIs 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 (95% Cis 96.0 days - 290.0 days; range: 89-651 days)
	High-Grade Recurrence Free Survival, % (95% CI)						
	Overall (n=133)	50 (41-59)	40 (31-48)	31 (23-40)	29 (21-37)	21 (13-28)	NR
	CIS ± Ta/T1 (n=93)	42 (31-52)	32 (22-41)	22 (13-31)	20 (11-28)	13 (6-21)	NR
	High-grade Ta/T1 alone (n=40)	69 (55-84)	59 (44-74)	53 (37-69)	50 (34-66)	37 (21-53)	NR
	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
	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
	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

	Time Point: Months	3	6	9	12	24	Median Duration of Response
	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[42,43,45]	***Complete Response Rate, n (%), 95% CI***						
	Overall	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	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	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
	Cystectomy						
	Overall	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

	Time Point: Months	3	6	9	12	24	Median Duration of Response
	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

Table D5. Safety I

Trial	Arms	N	Any AE	Any SAE	Treatment-related AE	Grade 3-5 AEs	Treatment-related AE Grade 3-5	Treatment-related SAEs	Discontinuation due to any AEs	Death
			n (%)							
Nadofaragene Firadenovec										
Phase III[33]	rAd-IFN	157	110 (70.1)	3 (1.9)	NR	6 (3.8)	NR	NR	3 (1.9)	0 (0)
Phase II SUO-CTC[34]	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[35]	Overall	17	17 (100)	1 (6)	NR	NR	NR	NR	0 (0)	3 (18)
Oportuzumab Monatox										
Phase III VISTA[37,40]	Overall	132	117 (88)	19 (14)	66 (50)	28 (21)	4 (3)	4 (3)	4 (3)	1 (<1)
Phase II Kowalski 2012[38]	Overall	45	43 (94)	6 (13)	30 (65)	9 (20)	3 (7)	0 (0)	0 (0)	0 (0)
Phase I Kowalski 2010[39]	Overall	64	41 (64)	0 (0)	20 (31)	0 (0)	1 (2)	0 (0)	0 (0)	1 (2)
Pembrolizumab										
Phase II KEYNOTE 057[42,43]	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[55]	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[47]	Gemcitabine	19	NR	NR	NR	NR	NR	NR	NR	NR
Gunelli 2007[48]	Gemcitabine	40	NR	NR	NR	NR	NR	NR	NR	NR
Perdona 2010[49]	Gemcitabine	20	NR	NR	NR	NR	NR	NR	NR	NR
Skinner 2013[50]	Gemcitabine	55	37 (67)	NR	NR	3 (5)	NR	NR	NR	8 (17)
Dalbagni 2002[51]	Gemcitabine	18	NR	NR	NR	NR	NR	NR	NR	NR

Trial	Arms	N	Any AE	Any SAE	Treatment-related AE	Grade 3-5 AEs	Treatment-related AE Grade 3-5	Treatment-related SAEs	Discontinuation due to any AEs	Death
			n (%)							
Dalbagni 2006[52]	Gemcitabine	30	NR	NR	NR	NR	NR	NR	NR	NR
Di Lorenzo 2010[56]	Cohort 1: Gemcitabine	40	15 Events	NR	NR	15 Events	NR	NR	NR	0 (0)
	Cohort 2: BCG	40	16 Events	NR	NR	16 Events	NR	NR	NR	1 (2.5)
Bartoletti 2005[113]	Gemcitabine	40	No difference was noted in terms of tolerability in the patients with BCG-refractory disease (P= 0.4863).							
Fiorito 2014[54]	Gemcitabine	41	NR	NR	NR	NR	NR	NR	NR	1 (2.4)
Sternberg 2013[57]	Gemcitabine	69	49 (71)	NR	NR	NR	NR	NR	NR (12)	26 (38)
Gemcitabine / Docetaxel										
Steinberg 2020[114]	Gemcitabine/ Docetaxel	276	112 (40.6)	26 (9.4)	NR	NR	NR	NR	9 (3.3)	44 (16)
Daniels 2020[61]	Gemcitabine/ Docetaxel	59	NR	NR	NR	NR	NR	NR	NR	NR
Steinberg 2015[63]	Gemcitabine/ Docetaxel	45	28 (62)	7 (16)	NR	NR	NR	NR	5 (11)	10 (4.5)
Milbar 2017[62]	Gemcitabine/ Docetaxel (Full Study Population)	33	NR	NR	NR	NR	NR	NR	2 (6)	3 (9)

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 averse event

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[33]	rAd-IFN	157	NR	NR	NR	NR	NR	NR	NR	NR	NR
Phase II SUO-CTC[34]	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[35]	Overall	17	NR (47)	NR (35)	NR	NR	NR	NR	NR	NR	NR (88)
Oportuzumab Monatox											
Phase III VISTA[37,40]	Overall	132	17 (13)	14 (11)	16 (12)	NR	43 (32)	34 (26)	33 (25)	NR	20 (15)
Phase II Kowalski 2012[38]	Overall	45	NR	NR	NR	NR	NR	23 (50)	6 (13)	NR	6 (13)
Phase I Kowalski 2010[39]	Overall	64	5 (8)	2 (3)	1 (2)	2 (3)	NR	9 (14)	7 (11)	NR	4 (6)
Pembrolizumab											
Phase II KEYNOTE 057[42,43]	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[55]	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[47]	Gemcitabine	19	NR	NR	NR	NR	NR	NR	NR	NR	NR
Gunelli 2007[48]	Gemcitabine	40	NR	NR	NR	NR	NR	37 (93)	0 (0)	NR	NR
Perdona 2010[49]	Gemcitabine	20	NR	NR	NR	NR	NR	2 (10)	NR	1 (5)	NR

Skinner 2013[50]	Gemcitabine	55	NR	NR	NR	NR	NR	NR	NR	NR	NR
Dalbagni 2002[51]	Gemcitabine	18	1 (6)	1 (6)	NR	NR	1 (6)	NR	5 (28)	1 (6)	7 (39)
Dalbagni 2006[52]	Gemcitabine	30	NR	NR	NR	1 (3)	1 (3)	9 (30)	1 (3)	NR	NR
Di Lorenzo 2010[56]	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
Bartoletti 2005[113]	Gemcitabine	40	No difference was noted in terms of tolerability in the patients with BCG-refractory disease (p=0.4863).								
Fiorito 2014[54]	Gemcitabine	41	NR	NR	NR	NR	NR	NR	NR	NR	NR
Sternberg 2013[57]	Gemcitabine	69	NR	NR	NR	1 (1.4)	NR	NR	NR	1 (1.4)	25 (36)
Gemcitabine / Docetaxel											
Steinberg 2020[114]	Gemcitabine/ Docetaxel	276	NR	NR	NR	NR	NR	7 (2.5)	2 (0.72)	NR	9 (3.3)
Daniels 2020[61]	Gemcitabine/ Docetaxel	59	NR	NR	NR	NR	NR	NR	NR	NR	NR
Steinberg 2015[63]	Gemcitabine/ Docetaxel	45	NR	3 (7)	NR	NR	1 (2.2)	15 (33)	5 (11)	NR	15 (33)
Milbar 2017[62]	Gemcitabine/ Docetaxel (Full Study Population)	33	4 (12)	NR	NR	NR	NR	NR	3 (9)	NR	Frequency: 7 (21) Urgency: 6 (18)

BCG: bacillus calmette guerin, mg: milligra**m**, 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[46]	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[33,115]	**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[34]	**BCG Refractory:** the inability to achieve a disease-free state at 6 months after adequate induction BCG therapy with	Adequate induction of BCG was defined as a minimum of five of six treatments, and adequate maintenance was	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

	either maintenance or reinduction at 3 months. **BCG Relapse:** recurrence within 1 year after a complete response to adequate BCG treatment	defined as a minimum of two of three treatments	concentration of IFNa-2b in the urine	
Phase I **Dinney 2013**[35]	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**[37,116]	**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**[38]	**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 of High-

			after being evaluated with repeat biopsy, directed and random.	Grade disease were withdrawn from treatment but were followed for survival and time to cystectomy.
Phase I Kowalski 2010 [39]	**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[42,43]	**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[55]	NR	NR	NR	NR
Allchorne 2014[47]	**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[48]	**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 last visit.

Perdona 2010[49]	**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[50]	**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[51]	NR	NR	Negative posttreatment cystoscopy including a biopsy of the urothelium and negative cytology	NR
Dalbagni 2006[52]	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[56]	**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
Bartoletti 2005[113]	**BCG-Refractory:** recurrence occurred within 6 months of starting BCG treatment	NR	NR	NR
Fiorito 2014[54]	NR	At least a complete induction of BCG	Negative cytology and cystoscopy at 12 months	NR

Sternberg 2013[57]	**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				
Steinberg 2020[114]	**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[61]	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[63]	**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
Milbar 2017[62]	**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.

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.[67]

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.

1. 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.[68]

2. 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).

3. 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.

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

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

6. 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	Usual Care	Source
Probability of Transitioning from MIBC to Post-Cystectomy	50.0%	50.0%	50.0%	Gore 2010[74]
Probability of Transitioning from MIBC to Metastatic Disease	3.9%	3.9%	3.9%	Griffiths 2011[75]
Probability of Transitioning from MIBC to Death	4.0%	4.0%	4.0%	Griffiths 2011[75]
Probability of Transitioning from Post-Cystectomy to Metastatic Disease	5.7%	5.7%	5.7%	Shariat 2006[76]
Probability of Transitioning from Metastatic Disease to Death	4.0%	4.0%	4.0%	Gore 2010[74]
Probability of Transitioning from Post-Cystectomy to Death	13.4%	13.4%	13.4%	von der Maase 2005[78]

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[83]
Pembrolizumab Administration Costs	Chemotherapy administration, intravenous infusion technique; up to one hour, single or initial substance/drug (CPT Code 96413)	$143	CMS.gov[83]

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

Treatment	Total Cost	QALYs	evLYG	Life Years	Time in Progression-Free State (Years)
Nadofaragene Firadenovec	$356,000	5.48	5.53	7.19	3.67
Oportuzumab Monatox	$344,000	5.45	5.51	7.16	3.65
Pembrolizumab	$310,000	5.38	5.43	7.08	3.56
Gemcitabine ± Docetaxel	$221,000	9.55	9.78	11.76	8.68
Usual Care	$223,000	4.99	4.99	6.64	3.10

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

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

Treatment	Total Cost	QALYs	evLYG	Life Years	Time in Progression-Free State (Years)
Nadofaragene Firadenovec	$358,000	5.78	5.90	7.50	3.94
Oportuzumab Monatox	$348,000	6.37	6.55	8.18	4.65
Gemcitabine ± Docetaxel	$222,000	10.24	10.48	12.50	9.45
Usual Care	$224,000	4.78	4.78	6.38	2.78

*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 and Oportuzumab Monatox at Assumed Placeholder 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	$128,350	$128,350	$111,555	$111,555
Year 2	$120,556	-$7,794	$103,908	-$7,647
Year 3	$114,742	-$5,814	$96,703	-$7,205
Year 4	$111,406	-$3,336	$91,296	-$5,407
Year 5	$110,426	-$980	$88,197	-$3,099