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

Revised Background and Scope

June 12, 2020

Background

Bladder cancer is the most common cancer involving the urinary system and usually presents with blood in the urine (hematuria). 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] Hematuria is typically painless and intermittent.[3] Individuals with bladder cancer can also have irritative symptoms such as frequency, urgency, or pain when urinating. Most patients have cancer confined to the bladder that is treated with limited surgical removal and local instillation of medicine into the bladder (intravesical). Bladder cancer has 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 of definitive surgery to entirely remove the bladder (cystectomy).[4,5] The overall cost of health care for those with bladder cancer is large, estimated to be $4-5 billion dollars in the US.[6]

The evaluation of patients with hematuria or urinary symptoms includes a history, physical examination, and tests. Bladder cancer increases with age and is more common in men than women. It is rare in those younger than 40 years old and diagnosis is most common in the late sixties or early seventies.[7] Thus, testing for bladder cancer should be considered in older individuals with macroscopic (visible to the eye) hematuria, urinary symptoms or asymptomatic microhematuria (only noted on testing) in the absence of an already identified causes.[8] 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 localized bladder cancer, initial treatment involves a procedure called transurethral resection of bladder tumor (TURBT) to remove identified tumors.

Treatment of bladder cancer is based upon staging that includes cystoscopy and 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).[9] Staging focuses on differentiating invasive and metastatic cancer from localized, non-muscle invasive bladder cancer (NMIBC). These 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 Tis, about 10%); and 3) cancers invading below the surface but not into the muscle of the bladder (submucosa or lamina propria, or T1, about 20%).[10] 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 but live form of Mycobacterium bovis, is the standard initial intravesical therapy. BCG and other intravesical treatments all cause bladder irritation that commonly results in pain, urinary frequency, and urgency. Moreover, these treatments are administered via a catheter into the bladder, which requires 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.[11] 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 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.[9] Given the morbidity and decreased quality of life associated with cystectomy, and limited data supporting bladder-preserving treatments in those with BCG-unresponsive disease, there is the need for new, bladder-preserving treatment options.

One new intravesical treatment uses a nonreplicating recombinant adenovirus vector that encodes the human interferon alfa-2b gene. Nadofaragene firadenovec (Adstiladrin®) uses Syn3, a polyamide surfactant, to enhance transfer of the recombinant adenovirus into cancer cells.[12] Another new target for intravesical treatment is the epithelial cell adhesion molecule (EpCAM) positive cancer cell.[13] Oportuzumab monatox (Vicinium®) is a recombinant fusion protein with a humanized anti-EpCAM single-chain antibody linked to *Pseudomonas* exotoxin A. Oportuzumab binds to the cancer cell and then releases the toxin into the cell, inducing cell death (apoptosis). Additionally, the systemic checkpoint inhibitor pembrolizumab (Keytruda®) that targets the programmed cell death protein 1 (PD-1) recently received approval by the FDA for use in patients with BCG-unresponsive NMIBC.[14]

Stakeholder Input

This scoping document was developed with input from diverse stakeholders, including patient advocacy organizations, clinicians, and manufacturers of the agents of focus in this review. This document incorporates feedback gathered during calls with stakeholders and open input submissions from the public. All stakeholders emphasized the need for new therapies for patients with NMIBC. Patients and patient advocacy organizations highlighted the impact of bladder cancer in terms of the difficult treatment decisions to be made, the wish to avoid cystectomy, the burden of treatment and follow-up testing, and the overall impact on quality of life. Clinicians and manufacturers discussed the limited treatment options for patients unable to have or wishing to avoid cystectomy and the ways that lack of consensus on study eligibility criteria and outcome measures have contributed to a lack of comparative data on available therapies. After publication of this scoping document, ICER looks forward to continued engagement with stakeholders throughout its review and encourages comments to refine our understanding of the clinical effectiveness and value of preventive treatments.

Report Aim

This project will evaluate the health and economic outcomes of nadofaragene firadenovec and oportuzumab monatox for BCG-unresponsive NMIBC. The ICER value framework includes both quantitative and qualitative comparisons across treatments to ensure that the full range of benefits and harms – including those not typically captured in the clinical evidence such as innovation, public health effects, reduction in disparities, and unmet medical needs – are considered in the judgments about the clinical and economic value of the interventions.

Scope of Clinical Evidence Review

The proposed scope for this assessment is described on the following pages using the PICOTS (Population, Intervention, Comparators, Outcomes, Timing, and Settings) framework. Evidence will be abstracted from randomized controlled trials and single-arm trials as well as high-quality systematic reviews; high-quality comparative cohort studies will be considered, particularly for long-term outcomes and uncommon adverse events. Our evidence review will include 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 will be synthesized qualitatively or quantitatively. Wherever possible, we will seek out head-to-head studies of the interventions and comparators of interest. Data permitting, we will also consider combined use of direct and indirect evidence in network meta-analyses of selected outcomes. Full details regarding the literature search, screening strategy, data extraction,

and evidence synthesis will be provided after the revised scope in a research protocol published on the Open Science Framework website (https://osf.io/7awvd/).

Populations

The population of focus for the review is adults with BCG-unresponsive/refractory, high risk NMIBC (CIS ± Ta/T1 or non-CIS with high grade Ta/T1).

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).[15]

Interventions

The full list of interventions is as follows:

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

Comparators

Data permitting, we intend to compare all the agents to each other and to:

- Intravesical therapy with gemcitabine with or without docetaxel
- Systemic pembrolizumab

Outcomes

The outcomes of interest are described in the list below.

- Patient-Important Outcomes
    - Quality of life
    - Mortality
    - Cystectomy
    - Metastatic disease
    - Recurrence requiring repeat treatment
    - Sexual function
    - Treatment burden

    - Adverse events including:
        - Infection
        - Lower urinary tract symptoms
        - Incontinence
        - Any adverse events leading to treatment discontinuation
        - Systemic side effects
- Other Outcomes
    - Progression-free survival
    - Complete response
    - Disease-free survival
    - Event-free survival
    - Recurrence (including type of recurrence, e.g., T1)
    - Duration of response
    - Adverse events including:
        - Development of antibodies to adenovirus
        - Shedding of adenovirus

Timing

Evidence on intervention effectiveness will be 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 will be considered, with a focus on outpatient settings in the US.

Potential Other Benefits and Contextual Considerations

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

Table 1.1. Potential Other Benefits or Disadvantages 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.
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

ICER encourages stakeholders to provide input on these elements in their public comment submissions.

Scope of Comparative Value Analyses

As a complement to the evidence review, we will develop an economic model to assess the lifetime cost effectiveness of nadofaragene firadenovec and oportuzumab monatox relative to intravesical therapy with gemcitabine with or without docetaxel and systemic pembrolizumab. The model structure will be based in part on a literature review of prior published models of bladder cancer, with a focus on bladder cancer in patients with BCG-unresponsive/refractory NMIBC.[16-20] The base-

case analysis will take a health care system perspective (i.e., focus on direct medical care costs only). Data permitting, productivity impacts and other indirect costs will be considered in a separate analysis. This modified societal perspective analysis will be considered as a co-base case when the societal costs of care are large relative to direct health care costs and the impact of treatment on these costs is substantial. This will most often occur in cases where the incremental cost-effectiveness ratio changes by greater than 20%, greater than $200,000 per QALY, and/or when the result crosses the threshold of $100,000-$150,000 per QALY gained. The target population will consist of adults 18 years and older with BCG-unresponsive/refractory NMIBC. Since this population is a selected group and depends on response to initial treatment with BCG, the modeled population will be representative of patients enrolled in clinical and single-arm trials of nadofaragene firadenovec and oportuzumab monatox.

The model will consist of health states including 1) initial treatment with nadofaragene firadenovec, oportuzumab monatox, or comparators; 2) disease-free; 3) persistent/recurrent NMIBC; 4) post-cystectomy; 5) muscle-invasive bladder cancer; 6) metastasis; and 7) death. Treatment-related adverse events leading to measurable disutility will also be considered for inclusion in the model. A cohort of patients will transition between states during predetermined cycles of three months over a lifetime time horizon, modeling patients from treatment initiation until death. In addition, cost effectiveness will be estimated for shorter time horizons (e.g., five years). Patients with differing BCG-unresponsive/refractory NMIBC classifications (e.g. CIS ± Ta/T1 or non-CIS with high grade Ta/T1) may be modeled separately due to differing effectiveness of treatments and/or probabilities of complications.

Key model inputs will include clinical probabilities, quality of life values, and health care costs. Probabilities, costs, and other inputs will differ to reflect varying effectiveness between interventions. Treatment effectiveness will be estimated using network meta-analysis or meta-analysis if sufficient data exist. If such data are not available, clinical trial data will be used directly to estimate treatment effectiveness.

Health outcomes and costs will be dependent on time spent in each health state, clinical events, adverse events (AEs), and direct medical costs. The health outcome of each intervention will be evaluated in terms of time in remission (in years), life years gained, quality-adjusted life years (QALYs) gained, and equal value of life years gained (evLYG). Quality of life weights will be applied to each health state, including quality of life decrements for serious adverse events. The model will include direct medical costs, including but not limited to costs related to drug administration, drug monitoring, condition-related care, and serious adverse events. In addition, productivity changes and other indirect costs will be included in a separate analysis if available data allow. Relevant pairwise comparisons will be made between treatments, and results will be expressed in terms of the marginal cost per QALY gained, cost per evLYG, cost per life year gained, and cost per year in

remission. Deterministic and probabilistic sensitivity analyses will be conducted to evaluate model uncertainty.

In separate analyses, we will explore the potential health care system budgetary impact of treatment over a five-year time horizon, utilizing published or otherwise publicly available information on the potential population eligible for treatment and results from the economic model for treatment costs and cost offsets. This budgetary impact analysis will indicate the relation between treatment prices and level of use for a given potential budget impact, and will allow assessment of any need for managing the cost of such interventions. More information on ICER's methods for estimating potential budget impact can be found here.

Identification of Low-Value Services

As described in its Value Assessment Framework for 2020-2023, ICER will include in its reports information on wasteful or lower-value services in the same clinical area that could be reduced or eliminated to create additional resources in health care budgets for higher-value innovative services (for more information, see ICER's Value Assessment Framework). These services are ones that would not be directly affected by novel intravesical therapies (e.g., delayed need for cystectomy), as these services will be captured in the economic model. Rather, we are seeking services used in the current management of bladder cancer beyond the potential offsets that arise from a new intervention. ICER encourages all stakeholders to suggest services (including treatments and mechanisms of care) that could be reduced, eliminated, or made more efficient.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. *CA Cancer J Clin.* 2020;70(1):7-30.
2. National Cancer Institute. Cancer Stat Facts: Bladder Cancer. 2019.
3. Peterson LM, Reed HS. Hematuria. *Prim Care.* 2019;46(2):265-273.
4. Brisbane WG, Holt SK, Winters BR, et al. Nonmuscle Invasive Bladder Cancer Influences Physical Health Related Quality of Life and Urinary Incontinence. *Urology.* 2019;125:146-153.
5. Winters BR, Wright JL, Holt SK, Dash A, Gore JL, Schade GR. Health Related Quality of Life Following Radical Cystectomy: Comparative Analysis from the Medicare Health Outcomes Survey. *The Journal of urology.* 2018;199(3):669-675.
6. Yeung C, Dinh T, Lee J. The health economics of bladder cancer: an updated review of the published literature. *Pharmacoeconomics.* 2014;32(11):1093-1104.
7. Malats N, Real FX. Epidemiology of bladder cancer. *Hematol Oncol Clin North Am.* 2015;29(2):177-vii.
8. Davis R, Jones JS, Barocas DA, et al. Diagnosis, evaluation and follow-up of asymptomatic microhematuria (AMH) in adults: AUA guideline. *The Journal of urology.* 2012;188(6 Suppl):2473-2481.
9. Flaig T, Spiess P, Agarwal N, et al. Bladder Cancer, Version 5.2020, NCCN Clinical Practice Guidelines in Oncology. 2020.
10. Kirkali Z, Chan T, Manoharan M, et al. Bladder cancer: epidemiology, staging and grading, and diagnosis. *Urology.* 2005;66(6 Suppl 1):4-34.
11. Kaufman DS, Shipley WU, Feldman AS. Bladder cancer. *Lancet.* 2009;374(9685):239-249.
12. Benedict WF, Tao Z, Kim C-S, et al. Intravesical Ad-IFNalpha causes marked regression of human bladder cancer growing orthotopically in nude mice and overcomes resistance to IFN-alpha protein. *Mol Ther.* 2004;10(3):525-532.
13. Di Paolo C, Willuda J, Kubetzko S, et al. A recombinant immunotoxin derived from a humanized epithelial cell adhesion molecule-specific single-chain antibody fragment has potent and selective antitumor activity. *Clin Cancer Res.* 2003;9(7):2837-2848.
14. Hahn NM, Necchi A, Loriot Y, et al. Role of Checkpoint Inhibition in Localized Bladder Cancer. *Eur Urol Oncol.* 2018;1(3):190-198.
15. Food and Drug Administration. *BCG-Unresponsive Nonmuscle Invasive Bladder Cancer: Developing Drugs and Biologics for Treatment.* 2018.
16. van Kessel KE, Kompier LC, de Bekker-Grob EW, et al. FGFR3 mutation analysis in voided urine samples to decrease cystoscopies and cost in nonmuscle invasive bladder cancer surveillance: a comparison of 3 strategies. *J Urol.* 2013;189(5):1676-1681.
17. Bachir BG, Dragomir A, Aprikian AG, et al. Contemporary cost-effectiveness analysis comparing sequential bacillus Calmette-Guerin and electromotive mitomycin versus bacillus Calmette-Guerin alone for patients with high-risk non-muscle-invasive bladder cancer. *Cancer.* 2014;120(16):2424-2431.
18. Wang Z, Xiao H, Wei G, et al. Low-dose Bacillus Calmette-Guerin versus full-dose for intermediate and high-risk of non-muscle invasive bladder cancer: a Markov model. *BMC Cancer.* 2018;18(1):1108.
19. Mossanen M, Wang Y, Szymaniak J, et al. Evaluating the cost of surveillance for non-muscle-invasive bladder cancer: an analysis based on risk categories. *World J Urol.* 2019;37(10):2059-2065.
20. Heijnsdijk EAM, Nieboer D, Garg T, Lansdorp-Vogelaar I, de Koning HJ, Nielsen ME. Cost-effectiveness of surveillance schedules in older adults with non-muscle-invasive bladder cancer. *BJU Int.* 2019;123(2):307-312.