Nadofaragene Firadenovec and Oportuzumab Monatox for BCG-Unresponsive, Non-Muscle Invasive Bladder Cancer: Final Policy Recommendations

December 17, 2020

Policy Recommendations

Introduction

The following policy recommendations reflect the main themes and points made during the Policy Roundtable discussion at the November 20, 2020 Midwest CEPAC public meeting on the use of nadofaragene firadenovec and oportuzumab monatox for the treatment of BCG-unresponsive non-muscle invasive badder cancer (NMIBC). At the meeting, ICER presented the findings of its revised report on these treatments and the Midwest CEPAC voting council deliberated on key questions related to their comparative clinical effectiveness, potential other benefits, and contextual considerations. Following the votes, ICER convened a Policy Roundtable of two patient advocates, two clinical experts, two payers, and two pharmaceutical manufacturer representatives to discuss how best to apply the evidence and votes to real-world practice and policy. The discussion reflected multiple perspectives and opinions, and therefore, none of the statements below should be taken as a consensus view held by all participants.

A recording of the conversation can be accessed here, and recordings of the voting portion of the meeting can be accessed here and here. More information on Policy Roundtable participants, including conflict of interest disclosures, can be found in the appendix of this document. ICER's final report on these treatments, which includes the same policy recommendations, can be found here.

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

Payers

Prior authorization criteria should be based on clinical evidence, specialty society guidelines, and input from clinical experts and patient groups. The process for authorization should be clear and efficient for providers. Options for specific elements of coverage criteria within insurance coverage policy are discussed below.

Clinical Considerations

Patient Eligibility Criteria

a. **Patient population:** Given that trials of nadofaragene firadenovec and oportuzumab monatox included only patients with BCG-unresponsive NMIBC, it would be expected for the FDA labels for both treatments to be limited to these patients. BCG-unresponsive NMIBC broadly includes patients with refractory disease while receiving treatment or those

with relapsing disease following at least two treatment courses. It is not clear whether the FDA labels will explicitly include "BCG-intolerant" patients, but clinicians are likely to view these patients as potentially eligible for treatment with the newer agents. Payers may therefore wish to consider requiring documentation of a trial of BCG as a criterion for coverage.

b. **Diagnosis:** Patients with BCG-unresponsive NMIBC were required to have had biopsy evidence of 1) carcinoma in situ (CIS) or 2) high grade papillary (Ta) or superficially invasive (T1) disease alone. Patients with CIS could also have Ta/T1 disease.
c. **Exclusion criteria:** Patients whose biopsy showed low/moderate grade Ta/T1 disease alone were excluded from the clinical trials. It is not yet known whether the FDA label will specify the pathological grade of NMIBC.

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

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

Manufacturers

Manufacturers should acknowledge that single-arm trials usually fail to provide the kind of evidence that is needed to help patients, clinicians, and insurers understand the comparative clinical effectiveness and value of new treatments. Manufacturers developing new treatments for BCG-unresponsive NMIBC should therefore use randomized trials as the basis for regulatory approval. Where this has not been done, manufacturers should sponsor real-world comparative

studies of their therapies that can help evaluate a broad set of patient-relevant outcomes including quality of life, work and disability status, and overall mortality.

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

Manufacturers should set prices for new therapies based on their demonstrated added clinical value over lower-cost clinically appropriate regimens. Leapfrogging these lower-cost regimens and setting prices in conjunction with higher-cost options adds to the growing financial toxicity of oncology care for patients today and in the future.

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

Patient Advocacy Organizations

Patient groups advocating for bladder cancer research and for patients with bladder cancer have played an essential role in bringing forward important new advances in care. These groups should continue their efforts to encourage innovation while pushing life science companies to generate better evidence to guide patient and clinician decision-making.

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

Patient groups should fully embrace their power to speak explicity about the impact of the high cost of treatments for BCG-unresponsive NMIBC. General statements of concern about "cost" shifts the focus subtly away from prices, which is consistent with the interests of the life science industry. Doing so deflects from the reality that drug makers have the power to set prices in the

United States and the result produces affordability concerns for health systems, financial toxicity for patients and families, and barriers to the ability of patients to gain access to optimal clinical care. Bladder cancer patient groups should be willing to name the problem and bear witness to the harms that excessive prices for new therapies cause.

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

Providers

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

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

Clinical and Specialty Societies

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

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

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

Regulators

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

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

Researchers

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

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

Researchers should develop comparative trials of BCG-unresponsive NMIBC that assess whether new medications have a lower risk of progression to cystectomy and other important patient outcomes over time.

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

Appendix

Appendix Tables 1 through 3 contain conflict of interest (COI) disclosures for all participants at the November 20, 2020 public meeting of the Midwest CEPAC.

Appendix Table 1. ICER Staff and Consultants and COI Disclosures

ICER Staff and Consultants	
Steven J. Atlas, MD, MPH* Director, Primary Care Research & Quality Improvement Network, Massachusetts General Hospital; Associate Professor of Medicine, Harvard Medical School	**Monica Frederick**,* Program and Event Coordinator, ICER
Molly Beinfeld, MPH,* Research Lead, Evidence Synthesis, ICER	**Avery McKenna,*** Research Assistant, ICER
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*No conflicts of interest to disclose, defined as individual health care stock ownership (including anyone in the member's household) in any company with a product under study, including comparators, at the meeting in excess of $10,000 during the previous year, or any health care consultancy income from the manufacturer of the product or comparators being evaluated.

Appendix Table 2. Midwest CEPAC Panel Member Participants and COI Disclosures

Participating Members of Midwest CEPAC	
Eric Armbrecht, PhD (Chair)* Associate Professor, Saint Louis University Center for Health Outcomes Research, School of Medicine and College for Public Health & Social Justice	**Yngve Falck-Ytter, MD, AGAF*** Professor of Medicine, Case Western Reserve University; Chief, Gastroenterology and Hepatology VA Northeast Ohio Healthcare System, Cleveland
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*No relevant conflicts of interest to disclose, defined as more than $10,000 in healthcare company stock or more than $5,000 in honoraria or consultancies during the previous year from health care manufacturers or insurers.

Appendix Table 3. Policy Roundtable Participants and COI Disclosures

Policy Roundtable Participant	Conflict of Interest
Stephanie Chisolm, PhD, Director of Education and Research, Bladder Cancer Advocacy Network	BCAN receives funding from FerGene and Merck.
Rachelle Dillon, PhD, Director, Clinical Operations, Sesen Bio	Dr. Rachelle Dillon is a full-time employee for Sesen Bio.
Leslie Fish, RPh, PharmD, Vice President of Clinical Pharmacy, IPD Analytics	Dr. Leslie Fish is a full-time employee of IPD Analytics.
John Gore, MD, MS, FACS, Associate Professor, Department of Urology; Adjunct Associate Professor, Department of Surgery, University of Washington	Dr. John Gore is an investigator for research sponsored by FerGene Pharmaceuticals unrelated to this review.
John W. McKnight, PharmD, BCPS, Vice President, HPS Clinical and Specialty Strategies, Humana	Dr. McKnight is a full-time employee of Humana.
Aaron Mitchell, MD, MPH, Assistant Attending, Medical Oncologist, Memorial Sloan Kettering Cancer Center	Dr. Aaron Mitchell has no financial conflicts to disclose.
Karen Sachse, RN, MSN, Patient Advocate	Karen Sachse has received honorarium for participating in a patient focus group for FerGene.
Kristen Wachsmuth, DHSc, MBA, Senior Director, Medical Affairs & Clinical Development, FerGene	Dr. Kristen Wachsmuth is a full-time employee of FerGene.