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May 29, 2020

Steven D. Pearson, MD
President
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Two Liberty Square, Ninth Floor
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Re: Institute for Clinical and Economic Review – Bladder Cancer Review Open Input Period
Dear Dr. Pearson,

On behalf of the Cancer Support Community (CSC), an international nonprofit organization that provides support, education, and hope to people impacted by cancer, we appreciate the opportunity to respond to the request for comments regarding ICER's draft background and scope for the upcoming review of the clinical effectiveness and value of nadofaragene firadenovec and oportuzumab monatox.

As the largest direct provider of social and emotional support services for people impacted by cancer, and the largest nonprofit employer of psychosocial oncology professionals in the United States, CSC has a unique understanding of the cancer patient experience. Each year, CSC serves more than one million people affected by cancer through its network of over 45 licensed affiliates, more than 170 satellite locations, and a dynamic online community of individuals receiving social support services. Overall, we deliver more than $50 million in free, personalized services each year to individuals and families affected by cancer nationwide and internationally. Additionally, CSC is home to the Research and Training Institute (RTI)—the only entity of its kind focused solely on the experiences of cancer patients and their loved ones. The RTI has contributed to the evidence base regarding the cancer patient experience through its Cancer Experience Registry, various publications and peer-reviewed studies on distress screening, and the psychosocial impact of cancer, and cancer survivorship. This combination of direct services and research uniquely positions CSC to provide valuable patient and evidence-informed feedback on ICER's value assessments.

As we have noted in previous comment letters, we believe that value assessment of therapies that are not yet or only recently approved by the FDA is premature. However, we also recognize ICER's commitment to such assessments and therefore, believe it is important to present the information we have learned from patients living with the disease. Again, we ask that ICER routinely revisit value assessments as further evidence evolves and incorporate real world evidence and patient experience data into all assessments.

As evidenced by our comments during the open input period, the potential impact on the quality of life of patients with bladder cancer is significant. While we recognize that quality of life is high on the list of "patient-important outcomes" in this scoping document, we encourage ICER to keep these issues at the forefront of this review. With limited options for patients living with high-risk non-muscle invasive bladder cancer that is unresponsive to BCG (intravesical chemotherapy, systemic checkpoint inhibitor immunotherapy, or radical cystectomy) and significant quality of life challenges, new options for treatment are critical. The potential to avoid cystectomy is of great value to patients who would otherwise live with the significant quality of life challenges associated with the procedure.

In patients with high-grade NMIBC, BCG is the standard treatment, and over 60% of tumors eventually re-occur (UroToday, 2019). Once re-occurrence happens, patients face cystectomy (complete bladder removal). Potential treatment options include: 1) an ileal conduit, or stoma, which includes an opening of the skin so that urine can drain into an external bag; 2) a continent cutaneous reservoir, or Koch or Indiana pouch, which creates an internal bladder substitute with a stoma. The patient manually empties the bladder reservoir using a catheter about 6 or 7 times a day; or 3) a neobladder, or internal bladder substitute that is connected to the patient's urethra. In men, cystectomy includes the removal of the prostate and seminal vesicles. In women, cystectomy includes removal of the uterus, ovaries, and part of the vagina (Mayo Clinic, n.d.).

Patients who have their bladders surgically removed face significant challenges in quality of life and activities of daily living. These include physical (urinary and bowel symptoms, risk of infection, skin irritation, stones), sexual (potential dysfunction, body image concerns, inability to orgasm or to become sexually aroused, vaginal dryness, vaginal stenosis, discomfort during intercourse, infertility), psychosocial (social and emotional challenges associated with the disease, treatment, and challenges outlined here, logistical (restriction in activities), and financial (expenses associated with the equipment and supportive care necessary) challenges of a life-long chronic health and stigmatized condition. Research has shown that quality of life in bladder cancer survivors is lower in all domains for function and symptom than the general population (Singer et al., 2013). NMIBC survivors have impaired physical, psychological, and social quality of life compared to the general population (Jung et al., 2019). Bladder cancer is associated with decreased emotional functioning when compared to the general population (Singer et al., 2013) and significantly worse mental health (Fung et al., 2014). Due to these quality of life challenges, some patients may choose to forgo treatment altogether.

In closing, thank you for the opportunity to submit these comments. We welcome the opportunity to engage in further discussions with you to ensure the patient experience is valued and all patients have access to high-quality health care. We ask that the evidence from our Cancer Experience Registry, which we presented in our open input comments, be utilized within the assessment. We look forward to commenting on the full assessment. If you have questions regarding our comments, or if we can serve as a resource, please reach out to me at Efranklin@cancersupportcommunity.org.

Sincerely,

Elizabeth F. Franklin, PhD, MSW
Executive Director, Cancer Policy Institute
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Response to ICER's Draft Scoping Document Regarding Nadofaragene Firadenovec and Oportuzumab Monatox for Bacillus Calmette-Guérin (BCG)-Unresponsive, Non-Muscle Invasive Bladder Cancer (NMIBC)

FerGene appreciates the opportunity to provide comments on the draft scoping document on nadofaragene firadenovec for BCG-unresponsive NMIBC, and respectfully recommends the following items be taken into consideration when finalizing the scoping document.

Comparators: ***FerGene recommends that ICER not consider intravesical therapy with gemcitabine with or without docetaxel as a relevant comparator, due to lack of comparable clinical data***

In the scoping document, ICER states that the relevant comparators for the BCG-unresponsive/refractory, high risk NMIBC population include "intravesical therapy with gemcitabine with or without docetaxel, or systemic pembrolizumab." We agree that pembrolizumab is a relevant comparator as it was recently approved by the FDA for the target population. It also had efficacy and safety data reported in a clinical trial with a population that is aligned with the FDA's BCG-unresponsive definition, and comparable to the population in the phase 3 nadofaragene firadenovec trial (NCT02773849).[1,2] However, intravesical therapy with gemcitabine with or without docetaxel is not FDA-approved for the same population. Moreover, the current evidence for intravesical therapy with gemcitabine with or without docetaxel are either observational in nature or in patients that are not comparable to those in the phase 3 trial of nadofaragene firadenovec. Available clinical evidence of gemcitabine comes from a mixed population with patients having low grade (LG) Ta/T1 (papillary) diseases, fewer than 2 courses of prior BCG (including BCG-naïve patients), and lower rates of BCG refractory:

- Gemcitabine without docetaxel: only one trial (SWOG S0353) included NMIBC patients who failed ≥2 prior courses of BCG treatment.[3] However, a close comparison of the trial populations suggests that patients in SWOG S0353 had less severe disease and thus, better prognoses after BCG therapy than patients enrolled in the phase 3 nadofaragene firadenovec trial.[1] For example, SWOG S0353 included patients with LG tumors (13%) and contained a lower proportion of patients with refractory disease (19% vs. 53%). Furthermore, patients in SWOG S0353 were not BCG-unresponsive by FDA definition[11] as they were allowed to have prior BCG up to 3 years before recurrence/study registration.
- Gemcitabine + docetaxel: no clinical trial data were identified for gemcitabine + docetaxel in NMIBC. Three retrospective studies have reviewed the use of gemcitabine combination therapy among NMIBC patients.[4,5,6] Patients in these studies had less severe disease and thus had better prognoses than those in the phase 3 nadofaragene firadenovec trial. All three studies included patients with LG tumors and/or ≤1 prior BCG course (Steinberg et al. 2015: 9% BCG naïve and 38% with 1 course; Milbar et al. 2017: 24% BCG naïve; Steinberg et al. 2020: 53% with 1 course). In addition, the evaluation schedule and outcome definitions in these studies differ from those in the phase 3 nadofaragene firadenovec trial. For example, Steinberg et al. 2015 used treatment success as the primary efficacy definition, which differs from the efficacy endpoints commonly used in NMIBC trials. In Milbar et al., there was no standard protocol informing how often patients were routinely followed for evaluation of response or recurrence. Moreover, none of these studies explained how recurrences were measured.

Existing literature have provided evidence on how differences in patients' characteristics and study design/conduct could affect the treatment outcomes. For example, patients with high-grade disease (e.g., G3 tumor) have significantly higher rates of progression to muscle-invasive disease than patients with

LG tumors (e.g., G1 tumor) (hazard ratio [95% confidence interval (CI)] for G3 vs. G1: 5.84 [2.86, 11.92]).[7] Additionally, patients with Ta/T1 (papillary) disease are more likely to achieve recurrence-free survival (RFS) compared to those with carcinoma in situ (CIS) (12-month RFS rate: 43.8% vs. 24.3%).[8] Furthermore, the number of prior BCG courses that patients received has an impact on patient outcomes. Based on a 2020 systematic literature review, the pooled 12-month response rates were 24% (95% CI: 16–32%) among trials with ≥2 prior BCG courses and 36% (95% CI: 25–47%) for those with ≥1 prior BCG courses.[9] Finally, real-world vs. clinical trial design could lead to different findings on treatment effects. The FDA has emphasized the limitation of using real-world studies to inform treatment effectiveness and has highlighted examples where the treatment effects identified in observational studies could not be reproduced in clinical trials or with very different effect sizes or directions.[10]

***Population*: FerGene recommends that ICER use the same population definition when compare patient outcomes across treatments**

In the scoping document, ICER states that "The population of focus for this review is adults with BCG-unresponsive/refractory, high risk NMIBC (CIS ± Ta/T1 or non-CIS with high grade Ta/T1). BCG-unresponsive populations include both patients who did not respond to a reasonable course of treatment with BCG or other chemotherapeutics and patients who had recurrence after treatment within a short period of time (six months)." In the FDA guidance, BCG-unresponsive disease is defined as at least one of the following: 1) persistent or recurrent CIS alone or with recurrent Ta/T1 disease within 12 months of completion of adequate BCG therapy; 2) recurrent high-grade Ta/T1 disease within 6 months of completion of adequate BCG therapy; or 3) T1 high-grade disease at the first evaluation following an induction BCG course.[11] In this context, adequate BCG therapy is defined as at least one of the following: 1) at least five of six doses of an initial induction course plus at least two of three doses of maintenance therapy; or 2) at least five of six doses of an initial induction course plus at least two of six doses of a second induction course[11].

Clinical practice treatment patterns vary versus the FDA BCG-unresponsive definition causing risk for assessing new treatment response. FerGene recommends that ICER follows the FDA BCG-unresponsive definition for potential comparisons across treatments within a homogeneous population.

As stated above, differences in patient population could significantly impact treatment outcomes. We believe it is not feasible to draw rigorous comparison between intravesical gemcitabine with or without docetaxel and nadofaragene firadenovec due to these differences.

If ICER were to conduct such comparisons, careful consideration and clarification are needed to properly account for these differences when evaluating the comparative effectiveness and safety across these treatments.

***Societal Perspective*: FerGene encourages ICER to incorporate the potential societal benefit of nadofaragene firadenovec in the assessment**

As bladder cancer is associated with substantial indirect costs, it will be important to fully account for these in the assessment from a societal perspective.[13] FerGene appreciates ICER's discussion of indirect costs and the potential to consider a modified societal perspective as a co-base case.

As an innovative treatment that is well-tolerated and only needs to be administered once every three months, nadofaragene firadenovec requires fewer treatment administrations and physician visits compared to some comparators. FerGene believes that these additional indirect benefits will allow for less disruption to patients' daily lives, which may positively impact their quality-of-life, work productivity/loss of income, and could further reduce caregiver burden. These additional benefits could

have even more favorable impact during the ongoing COVID-19 pandemic (or any potential future pandemic) by reducing potential patient exposure to infectious diseases in clinics and reduce exposure risks to caregivers and health care workers. This benefit is particularly important in the target population, who are often elderly with multiple underlying medical conditions and are at a higher risk for worse outcomes (including death).

Cost-Effectiveness Analysis (CEA) Model Structure*: *FerGene suggests ICER to clarify the terminologies used for health states and to adopt a three-month cycle length for the CEA model

In the scoping document, ICER proposes the following health states for the economic model: 1) initial treatment with nadofaragene firadenovec, oportuzumab monatox, or comparators; 2) remission; 3) disease progression; 4) post-cystectomy; 5) muscle-invasive bladder cancer; 6) metastasis; and 7) death. While FerGene agrees that the selected health states captured well the expected disease course of patients with BCG-unresponsive NMIBC, some of the terminology are not consistent with those used in this population. For example, the health state of BCG-unresponsive NMIBC patients who responded to treatment are usually described as 'disease-free' (vs. 'remission'). Moreover, disease progression in NMIBC could refer to both disease recurrence and progression to muscle-invasive bladder cancer or metastasis. To avoid potential confusion, we would suggest using '2) disease-free' for '2) remission', and '3) NMIBC recurrence' for '3) disease progression'.

ICER states in the scoping document that a cycle length of one month will be considered in the economic model. We would recommend using a three-month cycle length instead for the following reasons. First, the assessments in both the nadofaragene firadenovec and pembrolizumab trials are at three-month intervals. Since there is no assessment at a one-month interval, using a one-month cycle length will introduce additional assumptions and potential inaccuracy. Second, a cycle length of three months is commonly used in previously published economic models in NMIBC.[14-17]

Other considerations

Including valrubicin as a relevant comparator: We recommend ICER to include valrubicin as a relevant comparator in the assessment. Valrubicin was approved by the FDA in a similar population and with comparable outcome measures as that of the phase 3 nadofaragene firadenovec trial.[18,19] US payers are interested in the comparative evidence of FDA-approved therapies in comparable patient population.

Existing evidence gap on health utility values for bladder cancer: There are no well-established health utilities for bladder cancer. Though National Institute for Health and Care Excellence (NICE) has used utility values identified through a search of available literature in their de novo economic model, it acknowledged the lack of patient utility data. For example, some health utility estimates are based on physician inputs instead of patients.[20] In the context of NICE economic evaluation, when EQ-5D values are not available for utility estimation, it recommends to establish the valuation system based on the general public.[21] It argues that "The source of values has important implications for the value obtained. Patients, for example, tend to generate higher values than members of the general public for the same health states (at least for physical health). The main argument for using the general public to value health states hinges on the view that in a publicly funded health care system it is society's resources that are being allocated, and therefore it is the views of the general population that are relevant." Hence, we recommend conducting a scientifically sound valuation study using responses from the US general public to establish the health utilities for bladder cancer.

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May 29, 2020

Steven D. Pearson, MD, MSc, FRCP
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RE: Assess Treatment for Bladder Cancer

Dear Dr. Pearson:

Thank you again for the continued opportunity to provide comments on the proposed ICER analysis of bladder cancer treatments. At this time, we would like to provide feedback on the scoping document released on March 13, 2020.

1. Study Population

The proposed study population is generally appropriate. Patient eligibility criteria and baseline characteristics (e.g., history of BCG treatment) should be examined before any analyses. Differences observed should be considered and adjusted (if feasible) when conducting quantitative and qualitative comparisons across treatments to ensure appropriate interpretation of study results. All analyses and evaluations should be done separately for both a) patients with *CIS ± Ta/T1*, and b) patients with *high grade Ta/T1 (without CIS)*.

2. Comparator

Pembrolizumab is included in the current NCCN Guidelines for Bladder Cancer (Version 3.2020), based on an FDA-approved indication for the treatment of patients with BCG-unresponsive high-risk NMIBC with CIS with or without papillary tumors who are ineligible for or have elected not to undergo cystectomy [1-2]. For the analysis proposed by the draft scoping document, pembrolizumab would be a potentially relevant comparator only for the subgroup of patients with *CIS ± Ta/T1*. KEYNOTE-057 is ongoing, and data from cohort B (papillary disease without CIS) has not yet been reported.

Although salvage intravesical therapies used in clinical practice include gemcitabine and sequential gemcitabine/docetaxel, these are not recommended in the NCCN Guidelines for Bladder Cancer due to a lack of rigorously conducted clinical trials in a carefully selected BCG unresponsive patient population. A systematic literature review is required to gather evidence for intravesical gemcitabine with or without docetaxel to inform the appropriate comparisons.

3. Outcome

The proposed list of study outcomes captures most of the critical endpoints in this population. Mortality is a less meaningful efficacy endpoint for BCG-unresponsive/refractory, high-risk NMIBC patients,

given that the follow-up duration in clinical trials is very short compared with the median overall survival (OS) of these patients. Duration of response (DOR) for participants with CIS who achieve a complete response (CR) should be added as an outcome of interest. One challenge for the proposed analysis will be the difference in reported study endpoints and variations in outcome definitions between trials. For example, for patients with CIS+/- papillary tumors, DOR was reported for pembrolizumab, which was estimated using the Kaplan-Meier method [1-2]; in contrast, the durability of the CR was reported for nadofaragene firadenovec measured by 3/6/9/12-month HGRF survival [3]. It is crucial to use standardized definition of outcomes across trials while conducting comparative analyses.

4. Challenges and Considerations for Comparative Effectiveness Assessment

- *Single-arm trials with CRR and DOR endpoints* create great challenges.

The pivotal trials that evaluate the efficacy and safety of nadofaragene firadenovec, oportuzumab monatox, and pembrolizumab in this disease setting are all single-arm studies. Although single-arm trials are appropriate for BCG-unresponsive NMIBC to support a marketing application per the FDA Guidance [4], these non-randomized studies were not designed to demonstrate superiority or non-inferiority to other agents in a similar disease setting. The absence of head-to-head trials poses severe limitations and uncertainty in assessing comparative treatment effectiveness. Naïve indirect cross-trial treatment comparisons would be problematic and biased.

- *The lack of long-term OS data* presents a major challenge.

BCG-unresponsive NMIBC is characterized by high recurrence and progression rates, but low mortality. Thus, OS may not be a feasible efficacy endpoint. The proposed time horizon of at least six months for effectiveness evaluation will likely only capture early efficacy endpoints, such as complete response rate. Immature OS data can lead to spurious projections of survival in the cost-effectiveness analyses, especially in cancer studies [5].

- Consider the following as part of the evidence on comparative clinical effectiveness assessment:

Modes, frequency, delivery mechanism, and durations of administration that may have impact on real-world adherence: The FDA has granted an accelerated approval to an updated dosing schedule for pembrolizumab (Keytruda) to include an every-6-weeks (Q6W) option at 400 mg across all indications in adult patients [6]. Given the COVID-19 situation, the Q6W dosing (versus the previously approved Q3W dosing) will provide a convenient option for patients, without compromising efficacy and safety, which may have further implication on resource use.

Pembrolizumab provides unique mechanism of action to treat bladder cancer. Pembrolizumab is an IO systemic agent which may have an impact on controlling urothelial cancer cells anywhere in the body (e.g., ureters/renal pelvis, upper tract, lymph nodes). In contrast, nadofaragene firadenovec and oportuzumab monatox are local agents instilled into the bladder and require direct contact with the urothelium. With this distinction, differences in disease control beyond the bladder may exist, which may become more apparent with longer follow-up.

The impact of treatment on patients' health-related quality life (HRQoL) is an element to be considered when assessing the value of medicines. In KEYNOTE-057, patient-reported outcomes (PROs) were assessed using the Functional Assessment of Cancer Therapy-Bladder Cancer (FACT-Bl) questionnaire, Core Lower Urinary Track Symptom Score (CLSS), and European Quality of Life Instrument-5

Dimensions (EQ-5D) [7]. The FACT-Bl consists of general cancer-specific subscales (FACT-G) and a bladder cancer-specific subscale/symptom index. HRQoL and symptom scores were stable over time (from baseline to week 51) during treatment with pembrolizumab. At a prespecified analysis time point of week 45, 70.0% of patients had improved or stable FACT-G total scores from baseline, and 82.5% had improved or stable FACT-G Physical Well Being scores from baseline.

5. Considerations for Economic Modelling Approach

Pembrolizumab is the appropriate comparator for patients with CIS with or without papillary tumors. The economic model should be developed for patients with and without CIS, separately.

The term "disease progression" should be replaced with the phrase "persistent/recurrent high-risk NMIBC." This is because "disease progression" is unspecific and may include "MIBC" and "metastasis," thus yielding three proposed health states no longer mutually exclusive.

The published economic models for NMIBC cited in the draft scoping document [8-12] are not appropriate, as they focus on a different target population (i.e., BCG naïve population and first-line treatments). Ramamohan et al. (2014) developed an economic model for BCG-refractory HR NMIBC with *CIS*, *CIS + Ta/T1*, and HR *Ta/T1* subpopulations [13], which is most relevant in this setting.

It is also advisable to consider an alternative three-month cycle length commonly used in the literature [10-13]. Three-month cycle length reflects the response assessment and efficacy review schedules for treatments such as pembrolizumab in KEYNOTE-057.

While an uncertainty analysis was not described in the draft scoping document, sensitivity analyses beyond mere one-way sensitivities will be critical and should be included. Such analyses include probabilistic sensitivity and scenario analyses. Considerable uncertainties stem from indirect treatment comparisons based on single-arm trials, lack of long-term survival data, and uncertainty around model inputs. Therefore, a point estimate will not be sufficient for meaningful inference of cost effectiveness. Care to appropriately characterize the uncertainty associated with model inputs will be needed to generate meaningful probabilistic analyses.

Thank you again for this opportunity to provide comments, and we look forward to continuing this engagement throughout the evaluation period. If you have any questions, please feel free to contact me.

Sincerely,

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