



Headquarters:
734 15th Street NW, Suite 300, Washington DC 20005
202.659.9709 Phone 202.974.7999 Fax

Denver Office:
1355 S. Colorado Blvd., C-601, Denver, CO 80222
1-888-234-2468 Phone 202.974.7999 Fax

New York City Office:
165 West 46th Street, Suite 805, New York, NY 10036
917.305.1200 Phone 212.967-8717 Fax

Research & Training Institute:
520 Walnut Street, Philadelphia, PA 19106
267.295.3000 Phone 215.883.2580 Fax

October 15, 2020

Steven D. Pearson, MD
President
Institute for Clinical and Economic Review
Two Liberty Square, Ninth Floor
Boston, MA 02109

Re: Institute for Clinical and Economic Review – Bladder Cancer Draft Evidence Report

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 evidence report and voting questions regarding the clinical effectiveness and value of nadofaragene firadenovec and oportuzumab monatox for Bacillus Calmette-Guérin (BCG)-unresponsive, high risk non-muscle invasive bladder cancer (NMIBC). These intravesical therapies were evaluated in comparison to systemic pembrolizumab and intravesical therapy with gemcitabine with or without docetaxel.

As we have noted in previous letters, we believe this value assessment is premature, particularly as pricing is not yet available for nadofaragene firadenovec and oportuzumab monatox. ICER notes that this makes it “difficult to determine whether treatment for BCG-unresponsive high-risk NMIBC will be considered cost-effective.” ICER elected to substitute the annual price of pembrolizumab and noted that “as a result, determining an appropriate and fair health-benefit based price for this heterogenous group of patients will be difficult, made even more so by not having evidence on potential comparators.”

ICER recognizes the “profound impact of BCG-unresponsive NMIBC on quality of life” and the “large burden” placed on patients dealing with this disease. The disease is a chronic condition for many resulting in significant quality of life, logistical, psychosocial, and financial burdens for patients. We appreciate ICER's recognition of these burdens on both patients and caregivers. ICER states that guideline-concordant care includes radical cystectomy as the “gold standard treatment” yet it is often declined (due to quality of life issues) or unfeasible (due to comorbidities). While “few patients progressed to metastatic disease or died during the short follow-up period...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.” We recognize the need for longer term follow-up with patients treated with nadofaragene firadenovec and oportuzumab monatox, however we also wish to re-emphasize the critical quality of life components inherent for patients whose only treatment option is cystectomy. While disease recurrence or progression over time is a possibility, the trade-off for

patients who wish to avoid the significant health, quality of life, psychosocial, logistical, and financial issues that can accompany cystectomy must be seriously considered. As a result of this difficult decision for patients, overall survival may not be the endpoint of most concern for them and must be weighed alongside all of the issues that may accompany cystectomy.

An additional item of note is ICER's reference to the dosing schedule of nadofaragene firadenovec and that a less frequent schedule is "an advantage during the COVID-19 pandemic where minimizing office visits is desirable." ICER goes on to say that "it is also likely that decreased frequency of dosing will decrease the burden of treatment and travel-related costs for patients, as well as family and caregivers." We would like to emphasize that less onerous dosing schedules are likely desired by many patients and caregivers, regardless of the pandemic. While the risk of contracting COVID-19 in a clinical setting is certainly a warranted concern, it is important to recognize the impact of dosing frequency and setting when considering value.

Finally, we are resubmitting our open input comments on bladder cancer treatment as well as our Cancer Experience Registry findings to help inform the voting panel's deliberations on this review.

Each year approximately 81,400 people in the United States are diagnosed with bladder cancer and 17,980 people die from the disease (American Cancer Society, 2020). Seventy percent of cases will be NMIBC (UroToday, 2019). Bladder cancer is more common in men than women (American Cancer Society, 2019). However, there are concerns that women may be overlooked and diagnosed at later stages than men as they are more likely to die from the disease (Cancer.net, 2019). Approximately one in three bladder cancers spread to the bladder muscle and four percent of cases have metastasized (American Cancer Society, 2019). Black patients are more likely to present with metastatic disease (American Cancer Society, 2019) and are more than twice as likely than whites to die from the disease (Cancer.net, 2019). Additional special populations to consider include those who have chronic urinary tract infections, military veterans, firefighters, people who have used tobacco, and anyone exposed to chemicals associated with the disease (such as arsenic, aromatic amines, or diesel fuels) or the chemotherapy drug cyclophosphamide if used for long periods of time as well as radiation of the pelvis. Further, people living with Lynch syndrome, Cowden disease, or those with a mutation of the retinoblastoma (RB1) gene have an increased risk for the disease (American Cancer Society, 2019).

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.).



Headquarters:
734 15th Street NW, Suite 300, Washington DC 20005
202.659.9709 Phone 202.974.7999 Fax

Denver Office:
1355 S. Colorado Blvd., C-601, Denver, CO 80222
1-888-234-2468 Phone 202.974.7999 Fax

New York City Office:
165 West 46th Street, Suite 805, New York, NY 10036
917.305.1200 Phone 212.967-8717 Fax

Research & Training Institute:
520 Walnut Street, Philadelphia, PA 19106
267.295.3000 Phone 215.883.2580 Fax

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., 2018). 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.

Of the bladder cancer survivors who participated in CSC's Cancer Experience Registry, the mean age is 60 years, 54% identify as female, and 95% identify as white. In terms of staging, 4% were stage 0, 24% were stage I, 13% were stage II, 16% were stage III, and 20% were stage IV. An additional 22% did not answer regarding the stage of their disease. In terms of treatment setting, 33% were treated at an academic or comprehensive cancer center, 29% at a community hospital or cancer center, 2% at a Veterans hospital, and 12% at a private oncology practice. Approximately 93% of respondents underwent surgery for their cancer and 59% stated that they receive chemotherapy (which could have been BCG). Respondents also reported the following:

- **67%** reported being moderately to very seriously concerned about **cancer progressing or coming back**
- **61%** reported being moderately to very seriously concerned about **worrying about the future and what lies ahead**
- **54%** reported being moderately to very seriously concerned about **disruptions to work, school, or home life**
- **51%** reported being moderately to very seriously concerned about **eating and nutrition**
- **49%** reported being moderately to very seriously concerned about **exercising and being physically active**
- **49%** reported being moderately to very seriously concerned about **moving around (walking, climbing stairs, lifting, etc.)**
- **46%** reported being moderately to very seriously concerned about **body image**
- **46%** reported being moderately to seriously concerned about **feeling too tired to do the things they need or want to do**
- **46%** reported being moderately to very seriously concerned about **recent weight change**
- **45%** reported being moderately to very seriously concerned about **sleep problems**

- **42%** reported being moderately to very seriously concerned about **pain and/or physical discomfort**
- **41%** reported being moderately to very seriously concerned about **worrying about family, children, and/or friends**
- **41%** reported being moderately to very seriously concerned about **health insurance or money worries**
- **39%** reported being moderately to very seriously concerned about **intimacy, sexual function, and/or fertility**
- **39%** reported being moderately to seriously concerned about **feeling nervous or afraid**
- **34%** reported being moderately to very seriously concerned about **finding meaning or purpose**
- **32%** reported being moderately to seriously concerned that they **felt irritable**
- **29%** reported being moderately to very seriously concerned about **making a treatment decision**
- **27%** reported being moderately to very seriously concerned about **managing side effects of treatment**
- **27%** reported being moderately to seriously concerned about **feeling sad or depressed**
- **25%** reported being moderately to very seriously concerned about **problems in their relationship with their spouse or partner**
- **24%** reported being moderately to very seriously concerned about **finding reliable information about complementary or alternative practices**
- **20%** reported being moderately to very seriously concerned about **feeling lonely or isolated**
- **20%** reported being moderately to seriously concerned about **thinking clearly**
- **20%** reported being moderately to very seriously concerned about **preparing for the end of life**
- **17%** reported being moderately to very seriously concerned about **communicating with their doctor**
- **17%** reported being moderately to very seriously concerned about the **fear of dying**
- **10%** reported being moderately to very seriously concerned about **tobacco or substance use by themselves or someone in their house**
- **7%** reported being moderately concerned about **transportation to treatment and appointments**

We appreciate the opportunity to provide these comments and would be pleased to serve as a resource to your work. I can be reached at efranklin@cancersupportcommunity.org.

Sincerely,



Elizabeth F. Franklin, PhD, MSW
Executive Director, Cancer Policy Institute
Cancer Support Community Headquarters



Headquarters:
734 15th Street NW, Suite 300, Washington DC 20005
202.659.9709 Phone 202.974.7999 Fax

Denver Office:
1355 S. Colorado Blvd., C-601, Denver, CO 80222
1-888-234-2468 Phone 202.974.7999 Fax

New York City Office:
165 West 46th Street, Suite 805, New York, NY 10036
917.305.1200 Phone 212.967-8717 Fax

Research & Training Institute:
520 Walnut Street, Philadelphia, PA 19106
267.295.3000 Phone 215.883.2580 Fax

References

- American Cancer Society. (2020). *Key statistics for bladder cancer*. Retrieved from <https://www.cancer.org/cancer/bladder-cancer/about.html>.
- American Urological Association. (2019). *BCG shortage info*. Retrieved from <https://www.auanet.org/about-us/bcg-shortage-info>.
- Cancer.net. (2019). *Bladder cancer: risk factors*. Retrieved from <https://www.cancer.net/cancer-types/bladder-cancer/risk-factors>.
- Fung, C., Pandya, C., Guancial, E., Noyes, K., Sahasrabudhe, D. M., Messing, E. M., & Mohile, S. G. (2014). Impact of bladder cancer on health-related quality of life in 1,476 older Americans: a cross-sectional study. *Journal of Urology*, 192(3), 690-695.
- Mayo Clinic. (n.d.). *Bladder removal surgery (cystectomy)*. Retrieved from <https://www.mayoclinic.org/tests-procedures/cystectomy/about/pac-20385108>.
- Singer, S., Ziegler, C., Schwalenberg, T., Hinz, A., Gotze, H., & Schulte, T. (2013). Quality of life in patients with muscle invasive and non-muscle invasive bladder cancer. *Supportive Care Cancer*, 21(5), 1383-1393.

Steven D. Pearson, MD, MSc, FRCP
 President
 Institute for Clinical and Economic Review

RE: Draft Evidence Report of Non-muscle Invasive Bladder cancer (NMIBC) Treatments

Dear Dr. Pearson:

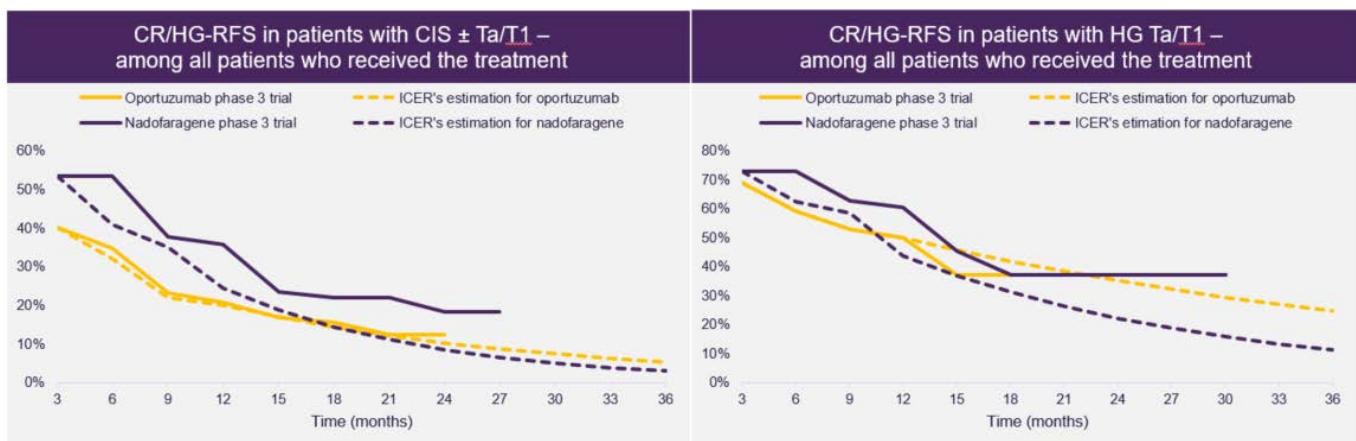
Thank you for the opportunity to provide feedback on ICER’s draft evidence report released on Sept 17, 2020. FerGene appreciates ICER's efforts and wishes to provide the following comments/suggestions:

1. The rates of complete response (CR)/high-grade recurrence-free survival (HG-RFS) for nadofaragene firadenovec in ICER’s cost-effectiveness analysis (CEA) is inconsistent with the clinical trial results

We urge ICER to use the estimates based on the complete long-term data from Kaplan-Meier (KM) curves of durability of response (DOR) to accurately inform the proportion of patients remaining in CR/ high-grade recurrence-free survival (HG-RFS) for nadofaragene firadenovec.¹ ICER’s current approach relied on incidence of RFS data over a short term. These estimates are rough approximation, have low precision and are inappropriate for model estimation as the actual proportion of patients remaining in CR/HG-RFS at each specific time point are not accurately reflected. In contrast, the DOR estimates have high precision. It reflects the proportion of patients who remain in CR/HG-RFS precisely at each month. In addition, the DOR curves included longer-term data: up to month 27 for the carcinoma in situ (CIS) ± Ta/T1 cohort, and up to month 30 for the HG Ta/T1 cohort, versus the 12-month data from incidence rates. The additional data over 12-month with the DOR curves provides better fit for the long-term trajectory of CR/HG-RFS.

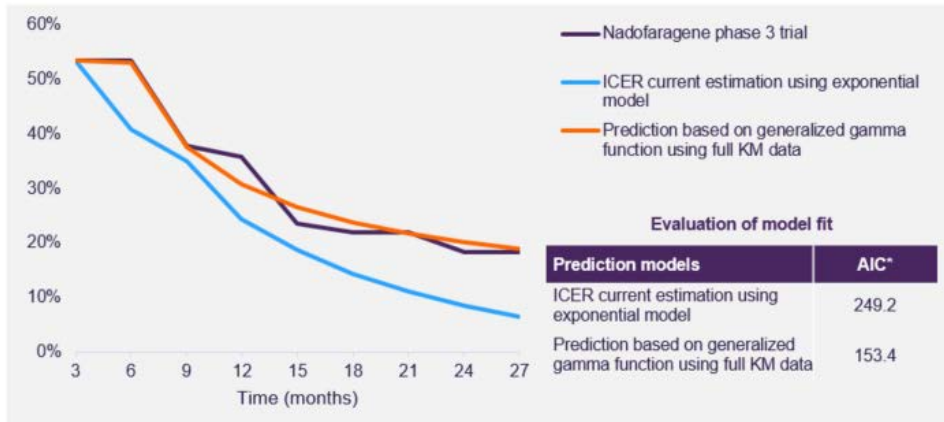
ICER’s current approach substantially underestimated nadofaragene firadenovec’s efficacy when compared to that using the KM curves of DOR. For example, at month 27, the deviation from the observed phase 3 trial data furthered to 61% (18% by KM curves vs. 7% by Incidence estimation).

ICER used inconsistent approaches to estimate the CR/HG-RFS rates for oportuzumab monatox and for nadofaragene firadenovec. For oportuzumab monatox, ICER used point estimates that matches the KM curves based on the trial observation. However, for nadofaragene firadenovec, ICER used the short-term incidence data, and as discussed above significantly underestimated the nadofaragene firadenovec’s efficacy and deviates substantially from the trial observation (see figure below for illustration).



For consistency and to use all available data that better reflect trial observations, we suggest ICER to apply the complete available long-term DOR KM data for both nadofaragene firadenovec and

oportuzumab monatox. In addition, we suggest that ICER select the generalized gamma model to extrapolate the long-term efficacy. ICER’s current approach only used two incidence data points to extrapolate the long term clinical probabilities after year 1, and arbitrarily applied the exponential model (i.e., $P=1-e^{-kt}$) to extrapolate the long-term efficacy. However, using Akaike information criterion (AIC), which is the most standard statistical method to evaluate model fit for non-linear parametric models and is widely used to select best-fit models by health technology appraisal agencies² and in prior ICER evaluations,^{3,4} the generalized gamma model is shown to fit the observed trial data much better than the exponential model (e.g., AIC 153.4 vs. 249.2, see figure below for illustration).



2. Nadofaragene firadenovec meets ICER’s definition of B+ evidence rating

ICER defines B+ rating as “Incremental or Better” – moderate certainty of a small or substantial net health benefit, with high certainty of at least a small net health benefit.

Nadofaragene firadenovec has been designated a breakthrough therapy and assigned a fast track designation by the Food and Drug Administration (FDA).⁵ The criteria for breakthrough therapy designation were based on clinical evidence demonstrating that nadofaragene firadenovec treatment results in substantial improvement on at least one clinically significant endpoint over available therapy.⁶

The FDA guidance for drug development in Bacille Calmette-Guerin (BCG) Unresponsive NMIBC states that “*Randomizing patients with BCG-unresponsive NMIBC to a placebo or minimally effective drug as a concurrent control raises ethical concerns. Currently, single-arm trials are appropriate for assessment of therapies for patients with BCG-responsive disease*”.

The efficacy of nadofaragene firadenovec has been demonstrated in clinical trials. In a phase 3 study, accepted for publication by Lancet Oncology, nadofaragene firadenovec reported CR/HG-RFS rates of 53.4% for CIS ± Ta/T1 patients and 72.9% for HG Ta/T1 patients at 3-month, and the durability of response among patients who achieved CR/HG-RFS is 41% in CIS ± Ta/T1 and 51% in HG Ta/T1 at 18 months.¹ The efficacy of nadofaragene firadenovec has exceeded the clinically meaningful thresholds suggested by the expert panel consensus that informed the FDA guidance on drug development for BCG unresponsive NMIBC patients.^{7,8} In a phase 2 study published at Journal of Clinical Oncology,⁹ nadofaragene firadenovec has demonstrated promising efficacy for patients with HG NMIBC after BCG therapy. Two phase 1 trials, published at Journal of Urology and Annals of Surgical Oncology, demonstrated that nadofaragene firadenovec is well tolerated with promising efficacy.^{10,11} The totality of the above evidence and information supports the B+ rating for nadofaragene firadenovec.

3. Medical costs of health states in BCG unresponsive NMIBC are significantly underestimated

We suggest that ICER use the more recent cost estimates based on SEER-Medicare data (Yang et al., 2020¹²) for medical costs of patients in the cost-effectiveness model. ICER used medical costs for

NMIBC recurrence and muscle-invasive bladder cancer (MIBC) collected in 1991-1999.^{13,14} Furthermore, the data were sourced from only 208 patients in a single medical center in Texas. The majority of the patients had less severe disease (only 28% with a prior history of recurrence) than HG BCG unresponsive NMIBC. The Yang et al. study, in contrast, has used more recent and more representative SEER-Medicare data (2008-2015), with medical costs reported specifically for HG NMIBC patients with adequate BCG treatments.¹² Estimates from Yang et al. (i.e., \$25,820 for NMIBC recurrence and \$59,774 for those with progression) are substantially higher than the annual cost estimates considered by ICER (i.e., \$5,832 for NMIBC recurrence and \$28,108 for MIBC).

4. Clearly label the comparator arm in the cost-effectiveness analysis (CEA) as “hypothetical treatment” instead of “usual care” to avoid confusion and potential misinterpretation

ICER used a hypothetical comparator arm in the CEA and “*intentionally left this comparator undefined.*” However, ICER labeled this hypothetical treatment arm as “usual care” in its draft evidence report. The term could be highly misleading as this is not the “usual care” in real clinical practice. The term “hypothetical treatment” should be used instead of “usual care” to correctly characterize the comparator arm used in CEA. In addition, due to the hypothetical nature of the comparator arm in the CEA, ICER should clearly state the limitations of its CEA results in guiding real world decision making.

5. Present the clinical effectiveness evidence and cost-effectiveness results by comparable study design and patient population to avoid potential “apple to orange” comparison

In the draft evidence report, ICER acknowledged “*differences in patient populations and study design make any direct comparisons exceedingly difficult.*” ICER also recognized that heterogeneity in patient characteristics could lead to differences in expected treatment outcomes. For example, ICER mentioned that “*failure types such as BCG-relapsing are associated with better outcomes compared with other reasons for BCG failure.*” ICER also acknowledged that prior treatments and their intensity could “*lead to differences among studies in terms of patients and how resistant to subsequent treatment their NMIBC is likely to be.*” However, in the draft evidence report, ICER summarized the efficacy results from various treatments in one table (Table 4.16) without clear separation by study design nor by patient population. Retrospective observational study with much less severe disease than BCG unresponsive are grouped together with clinical trials with BCG unresponsive NMIBC patients. Similarly, for cost-effectiveness assessment, the results are summarized in tables (Tables 5.10-5.13) for various treatments with very different study design and patient population. To avoid misinterpretation, a modified table format that clearly states the differences in study design and patient population is needed. In addition, statements should be added to the tables to clearly state that the differences in patient characteristics and study design could significantly affect study outcomes independent of the treatments and any comparison of efficacy across different study designs and/or patient population is not warranted. Below are suggested mock table templates (Tables 1-3) for ICER’s considerations:

Table 1. Mock table template for Table 4.16

Trial	Intervention	Population	CR at 3 months, n (%)	HGRFS at 12 months, n (%)	Median duration of response	Discontinuation due to any AE
<i>Prospective Clinical Trials of HG/HR BCG Unresponsive (at least 2 prior BCG) NMIBC Patients</i>						
Phase III	Nadofaragene firadenovec	Overall	59.60%	30.50%	NR	1.90%
		CIS± HG Ta/T1	53.40%	24.30%	NR	
VISTA	Opportuzumab monatox	Overall	NR	29%	NR	3.80%
		CIS± HG Ta/T1	40%	20%	287 days (9.6 months)	

Keynote 057	Pembrolizumab	CIS± HG Ta/T1	40.60%	NR	16.2 months	9.80%
<i>Prospective Clinical Trial of Mixed NMIBC Patients (Dalbagni 30% only 1 prior BCG course; Skinner 11% LG)</i>						
Dalbagni et al. (2006); Skinner et al. (2013)	Gemcitabine	Overall	40-50%	21-28%	3.6 -6.1 months	12%
<i>Retrospective Observational Study of Mixed NMIBC Patients (13% LG, 53% only 1 prior BCG course, 38% classified as BCG unresponsive)</i>						
Steinberg et al. (2020)	Gemcitabine with docetaxel	Overall	NR	60-69%	NR	9.40%

Table 2. Mock table template for Table 5.10-5.11

Treatment	Drug cost (per year)	Total cost	QALYs	evLYGs	Life years	Time in progression-free state (years)
<i>Results Based on Prospective Clinical Trials of HG/HR BCG Unresponsive (at least 2 prior BCG) NMIBC Patients</i>						
Nadofaragene firadenovec						
Oportuzumab monatox						
Pembrolizumab						
<i>Results Based on Retrospective Observational Study of Mixed NMIBC Patients (13% LG, 53% only 1 prior BCG course, 38% classified as BCG unresponsive)</i>						
Gemcitabine ± docetaxel						
<i>Results for Hypothetical Comparator (Based on Assumptions)</i>						
Usual care						

Table 3. Mock table template for Table 5.12-5.13

Treatment	Comparator	Cost per QALY gained	Cost per evLYG	Cost per LYG	Cost per year in progression-free state
<i>Results Based on Prospective Clinical Trials of HG/HR BCG Unresponsive (at least 2 prior BCG) NMIBC Patients</i>					
Nadofaragene firadenovec	Usual Care				
Oportuzumab monatox	Usual Care				
Pembrolizumab	Usual Care				
<i>Results Based on Retrospective Observational Study of Mixed NMIBC Patients [13% LG, 53% only 1 prior BCG course, 38% classified as BCG unresponsive]</i>					
Gemcitabine ± docetaxel	Usual Care				

6. Include full and complete adverse event (AE) and associated costs in CEA

ICER arbitrarily included only three common non-grade 3-5 AEs (i.e., urinary tract infection, rash, and pruritus) in the CEA for oportuzumab monatox and pembrolizumab. However, as presented in the clinical effectiveness section Table 4.6 (P22) and Table 4.9 (P26) in ICER’s draft evidence report, 21% patients treated with oportuzumab monatox and 29% patients treated with pembrolizumab experienced grade 3-5 AEs. ICER’s current approach to model AE and the associated costs substantially underestimated the cost of treating grade 3-5 AEs, and could be highly misleading on the safety of the treatments without including the full and complete serious AEs and associated costs. Corrections are needed in ICER’s revised CEA model to fully account for these AEs and associated costs.

Some inconsistent numbers are noticed in ICER’s draft evidence report as well. For example, the type of AEs and their proportions used in the CEA are inconsistent with the numbers reported in the clinical effectiveness section of the draft evidence report for oportuzumab monatox, and the US Prescribing Information (USPI) for pembrolizumab. For oportuzumab monatox, the clinical effectiveness section

reported 32% of patients have urinary tract infection (P22), while the CEA considered 12% of patients with this event. Many common AEs that were highlighted in the clinical effectiveness section or the USPI for pembrolizumab were not considered in the CEA, including: fatigue (29%), diarrhea (24%), hematuria (19%), cough (19%), arthralgia (14%), nausea (13%), constipation (12%), peripheral edema (11%), hypothyroidism (11%), and nasopharyngitis (10%) for pembrolizumab; and pain or burning on urination (26%) and hematuria (25%) for oportuzumab monatox.

7. Comments on the draft voting questions

Before the voting questions, clearly defined best supportive care is needed for both the voting panel and the public to make informed decisions. Additionally, clear evidence summaries on the efficacy, safety, tolerability, patient adherence/discontinuation, and frequency of administration for nadofaragene firadenovec, oportuzumab monatox, pembrolizumab, gemcitabine with or without docetaxel, and best supportive care, separated by study design and patient population, are needed before the voting questions. Strength/source of the evidence needs to be provided, e.g. peer-reviewed journal publication, congress presentations, investor report/social media postings, number of patients included in the study.

For draft voting questions 1 - 7, substitute the “net health benefit” with efficacy, safety, tolerability, patient discontinuation, and frequency of administration, respectively, to better inform the various aspects of the differences in treatments. e.g. expand question 1 into 1a – 1e as follows:

- 1a. Is the evidence adequate to demonstrate that the efficacy of nadofaragene firadenovec (Adstiladrin®, FerGene) is superior to that provided by best supportive care?
- 1b. Is the evidence adequate to demonstrate that the safety of nadofaragene firadenovec (Adstiladrin®, FerGene) is superior to that provided by best supportive care?
- 1c. Is the evidence adequate to demonstrate that the tolerability of nadofaragene firadenovec (Adstiladrin®, FerGene) is superior to that provided by best supportive care?
- 1d. Is the evidence adequate to demonstrate that the patient discontinuation of nadofaragene firadenovec (Adstiladrin®, FerGene) is superior to that provided by best supportive care?
- 1e. Is the evidence adequate to demonstrate that the frequency of administration of nadofaragene firadenovec (Adstiladrin®, FerGene) is superior to that provided by best supportive care?

Before the Potential Other Benefits and Contextual Considerations section of the voting questions, provide the following summary table to better inform the voting panel and the public:

- Unmet need in HG BCG unresponsive NMIBC
- Cost-effectiveness threshold as reference points for cost-effectiveness determinations
- The levels of absolute quality-adjusted life-year (QALY) measure or proportional QALY shortfall that would be considered small/medium/large health loss

8. Other suggestions

- *Table 4.2 in the draft report:* Nadofaragene firadenovec has reported the 12-month HG-RFS without mandatory biopsy as follows: CIS ± Ta/T1: 28 (27.2%); HG Ta/T1: 23 (47.9%).¹ These numbers should be included for consistency as the numbers reported for other new treatments are measured without mandatory biopsy
- *P18:* Update the Progression to MIBC section to: “8 (5.3%) of 151 patients in the overall study population progressed to muscle-invasive bladder cancer (MIBC) during the full available follow-up (median of 23.62 months)”
- *Table 4.10:* Revise the proportion of patients with low-grade Ta/T1 only from Skinner et al. (2013) publication to 11% (5/47).

REFERENCES

1. Boorjian SA, Alemozaffar M, Konety BR, et al. (in press). Intravesical nadofaragene firadenovec gene therapy for BCG-unresponsive nonmuscle invasive bladder cancer: a single-arm, open-label, repeat-dose clinical trial. *Lancet Oncol*.
2. National Institute for Health and Clinical Excellence (NICE) Decision Support Unit. NICE DSU technical support document 14: Survival analysis for economic evaluations alongside clinical trials - extrapolation with patient-level data. 2013; <http://nicedsu.org.uk/wp-content/uploads/2016/03/NICE-DSU-TSD-Survival-analysis.updated-March-2013.v2.pdf>. Accessed October 7, 2020.
3. Institute for Clinical and Economic Review (ICER). Chimeric antigen receptor T-cell therapy for B-cell cancers: Effectiveness and value (final evidence report). 2018; https://icer-review.org/wp-content/uploads/2017/07/ICER_CAR_T_Final_Evidence_Report_032318.pdf. Accessed October 7, 2020.
4. Institute for Clinical and Economic Review (ICER). Poly ADP-ribose polymerase (PARP) inhibitors for ovarian cancer: Effectiveness and value (final evidence report). 2017; https://icer-review.org/wp-content/uploads/2017/02/MWCEPAC_OVARIAN_FINAL_EVIDENCE_REPORT_10112017-1.pdf. Accessed October 7, 2020.
5. Ferring Pharmaceuticals. Ferring and Blackstone Life Sciences invest over \$570 million USD in novel gene therapy for bladder cancer patients. 2019; <https://www.ferringusa.com/press/ferring-and-blackstone-life-sciences-invest-over-570-million-usd-in-novel-gene-therapy-for-bladder-cancer-patients/>. Accessed October 7, 2020.
6. United States Food and Drug Administration. Breakthrough therapy. 2018; <https://www.fda.gov/patients/fast-track-breakthrough-therapy-accelerated-approval-priority-review/breakthrough-therapy>. Accessed October 7, 2020.
7. United States Food and Drug Administration. BCG-unresponsive nonmuscle invasive bladder cancer: Developing drugs and biologics for treatment (guidance for industry). 2018; <https://www.fda.gov/media/101468/download>. Accessed October 7, 2020.
8. Jarow JP, Lerner SP, Kluetz PG, et al. Clinical trial design for the development of new therapies for nonmuscle-invasive bladder cancer: report of a Food and Drug Administration and American Urological Association public workshop. *Urology*. 2014;83(2):262-264.
9. Shore ND, Boorjian SA, Canter DJ, et al. Intravesical rAd-IFN α /Syn3 for patients with high-grade, bacillus calmette-guerin-refractory or relapsed non-muscle-invasive bladder cancer: a phase II randomized study. *Journal of Clinical Oncology*. 2017;35(30):3410.
10. Dinney CP, Fisher MB, Navai N, et al. Phase I trial of intravesical recombinant adenovirus mediated interferon- α 2b formulated in Syn3 for Bacillus Calmette-Guérin failures in nonmuscle invasive bladder cancer. *The Journal of urology*. 2013;190(3):850-856.
11. Navai N, Benedict WF, Zhang G, et al. Phase 1b trial to evaluate tissue response to a second dose of intravesical recombinant adenoviral interferon α 2b formulated in syn3 for failures of bacillus Calmette-Guerin (BCG) therapy in nonmuscle invasive bladder cancer. *Annals of surgical oncology*. 2016;23(12):4110-4114.
12. Yang M, Georgieva MV, Bocharova I, et al. PCN62 Disease burden associated with progression in patients with high-grade non-muscle invasive bladder cancer receiving bladder preserving therapies after adequate BCG induction: A SEER-Medicare database study. *Value in Health*. 2020;23:S34.
13. 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.

14. Avritscher EB, Cooksley CD, Grossman HB, et al. Clinical model of lifetime cost of treating bladder cancer and associated complications. *Urology*. 2006;68(3):549-553.

Oct 15, 2020

Steven D. Pearson, MD, MSc, FRCP
President
Institute for Clinical and Economic Review
One State Street, Suite 1050
Boston, MA 02109 USA

RE: Assess Treatment for Bladder Cancer

Dear Dr. Pearson:

Thank you for the opportunity to continue providing feedback on the ongoing ICER assessment of bladder cancer. Please find below our comments on the draft evidence report and the draft voting questions released on September 17, 2020, as well as the cost-effectiveness model developed by University of Illinois at Chicago and shared on September 24, 2020.

1 Calculate the transition probabilities from NMIBC to MIBC for pembrolizumab based on treatment-specific progression free survival (PFS)

Recommendation: We strongly recommend revising the transition probability from NMIBC to MIBC for pembrolizumab from 2.40% to 1.36%, estimated based on the published 12-month pembrolizumab-specific PFS of 96.9% [1]. The input calculation for pembrolizumab is detailed in Appendix Table 1.

Concerns and Rationales: PFS is an important factor in determining the incremental cost effectiveness of treatments. We have significant concern that the current analysis was based on incorrect transition probabilities from NMIBC to MIBC for pembrolizumab, resulting in inaccurate clinical effectiveness and cost-effectiveness results.

- The average of the transition probabilities based on the PFS for the two intervention drugs was used as a proxy to populate the transition probability for pembrolizumab in the draft report, assuming that PFS data for pembrolizumab was not available. In fact, the 12-month PFS for pembrolizumab was reported as 96.9% [1] and thus should be used to populate this transition probability. This point was raised in our response to ICER's model development plan on August 21, 2020 (refer to section 1.8).
- Using the transition probability (1.36%) derived from the published 12-month PFS for pembrolizumab is more appropriate than what was used in the draft report (2.4%), because the former approach leads to a predicted PFS curve more aligned with the observed PFS curve from the clinical trial KN057 than that of the latter approach (Appendix Figure 1).
- Pembrolizumab should have the lowest transition probability (1.36%), compared with nadofaragene firadenovec (2.2%), and oportuzumab monatox (2.6%), because pembrolizumab had the highest 12-month PFS (96.9%) vs. nadofaragene firadenovec (95.1%) and oportuzumab monatox (94%).

2 Calculate the transition probabilities from Complete Response (CR) to NMIBC for pembrolizumab based on duration of response (DOR)

Recommendation: We strongly recommend using median DOR to derive the time-constant transition probability for pembrolizumab. For consistency, this approach should also be applied to the two interventions and other comparators when median DORs are available from the respective trials. The recommended inputs for pembrolizumab (base case and 2 alternative scenarios) are presented in Appendix Table 2.

Note that this approach could still be conservative in estimating pembrolizumab's long-term effectiveness, given the possible durable treatment effect implied by the flattened tail observed in the DOR curve beyond 12 months from KEYNOTE-057 (Appendix Figure 2).

Concerns & Rationales:

- First, pessimistic assumption was made in the draft report when interpreting the complete response data. When the number of patients in CR reduces over time, as shown by “number at risk”, it can be due to either an event (loss of CR) or a censor (e.g., reach the end of study cutoff, start new treatments, or have non-evaluable assessments), as illustrated in Appendix Figure 2 and Figure 3 [2]. The current approach pessimistically assumes that all censored patients experienced recurrence, which overestimates the transition probabilities from CR to NMIBC. With this approach, the median DOR that the model predicted for pembrolizumab (12 months, as shown in Appendix Table 3) is much shorter than what was reported from the KEYNOTE-057 (16.2 months), indicating that the current model lacks internal validity. We recommend using KM estimates, as illustrated in Appendix Table 2, as KM estimation is a typical approach to deal with censoring.
- Second, inconsistent approaches were used for populating the transition probabilities from CR to NMIBC for the CIS population in the draft report. Specifically, percentages of patients in CR over time were used for pembrolizumab, whereas high-grade recurrence free survival (HGRFS) probabilities were used for other regimens. According to the FDA guidance, CR and DOR are the recommended primary efficacy endpoints for patients with high-risk NMIBC with CIS since these patients have active disease at baseline, whereas recurrence-free survival is recommended for patients without CIS (as disease was resected before trial entry) [3].
- We have major concerns that using inconsistent approaches for calculating the transition probabilities have led to model predictions that are contradictory with the trial efficacy results. Specifically, the model predicts lower LY and QALY for pembrolizumab (6.22, 4.74, respectively) compared to those for oportuzumab monatox (6.28, 4.80), which was inconsistent with the clinical trial results that pembrolizumab had a slightly higher CR at 3 months (40.6% vs. 40%), and much longer median DOR (16.2 vs. 9.6 months) than oportuzumab monatox. Appendix Table 4 demonstrates that different transition probabilities (from CR to NMIBC) were derived for the same treatment (i.e., oportuzumab monatox), when calculated using difference approaches (i.e., CR and HGRFS, respectively).

- To deal with the above-mentioned censoring, endpoint and consistency issues, we strongly recommend using CR and DOR KM estimates (specifically median DOR) to derive the transition probabilities from CR to NMIBC for pembrolizumab and other interventions.

3 Remove the cost-effectiveness analysis of gemcitabine ± docetaxel in CIS population

Recommendation: We propose to remove the cost-effectiveness analysis of gemcitabine ± docetaxel for the CIS population until robust data become available.

Concerns and Rationales:

- Gemcitabine ± docetaxel are not appropriate comparators for the CIS population. These regimens are not recommended in the clinical guidelines for this population due to a lack of rigorously conducted clinical trials in this setting.
- The studies identified via the literature review were all retrospective in nature; some included a heterogenous population of patients (i.e., a mix of CIS and non-CIS patients) with varying risks of recurrence and progression. These limitations make it impossible to draw robust conclusion on the comparative efficacy of gemcitabine ± docetaxel versus usual care for the CIS population, and thus invalidates the cost-effectiveness analysis.
- The cost-effectiveness analysis for the CIS population relied heavily on one retrospective study [4] to inform efficacy inputs for gemcitabine ± docetaxel. Key issues included:
 - It is inappropriate to use the 3-month HGRFS as a proxy for the CR rate, as explained above under point 2. However, CR rates and DOR were not reported from the study, making it impossible to populate the model in a consistent way as other regimens.
 - The adjustment factor (rate ratio) used in the draft report lacks clinical justification. The rate ratio calculation was arbitrary and can vary by the selected time points. In addition, the adjustment factor was derived from an overall population, and thus not applicable to the CIS sub-population.
 - Efficacy inputs were solely based on studies for gemcitabine plus docetaxel, and therefore should not be used to represent the efficacy for gemcitabine without docetaxel.
- The significant limitation of the data and the use of inappropriate endpoint have led to clinically implausible predictions of the model in the draft report. Specifically, the model predicted that gemcitabine ± docetaxel has a median DOR of 4 years, and that patients on average would stay in CR for 5 years during an average of 11 life years (Appendix Table 3). These model results are not aligned with clinical insights and other published data, which suggested much lower efficacy for gemcitabine ± docetaxel [5].
- Two additional impactful calculation errors are described in Appendix Table 5.

4 Revise key model inputs (i.e., drug cost and transition probability from CR to NMIBC at 6 months) for oportuzumab monatox

Recommendation: The following model inputs for oportuzumab monatox should be revised.

- The frequency of drug administration was inconsistently reported in different sections in the draft report. The correct dosing schedule is every other week for maintenance [6].

- The drug cost for oportuzumab monatox should be \$4,317 per dose (instead of \$2,826 per dose in the draft report), calculated based on the total number of doses of 38 per year (instead of 58 per year in the draft report).
- The transition probability from CR to NMIBC at 6 months for oportuzumab monatox should be 23.8% (instead of 20% used in the draft report). It should be calculated as $(1 - 32\%/42\%)*100\% = 23.8\%$.

5 Comments on comparison between pembrolizumab and treatments other than usual care

Recommendation: We propose to remove the sentence (page 69) on the draft report, that for pembrolizumab, ‘the QALY gains appeared to be smaller than those seen with any of the other treatments’.

Rationales: This statement implies to compare the clinical effectiveness of pembrolizumab with nadofaragene firadenovec, oportuzumab monatox, and gemcitabine \pm docetaxel. This contradicts the conclusion from the draft report around large uncertainties in comparative benefits and harms among pembrolizumab and other therapies (see Section 4.4, Comparative Clinical Effectiveness). Thus, it is premature to compare and draw any conclusions on QALY comparison between pembrolizumab and other therapies.

Again, we would like to thank ICER for the opportunity to provide comments. We are looking forward to continuing this engagement throughout the evaluation period.

Sincerely,



Ravinder Dhawan, PhD
Vice President, CORE Oncology
Center for Observational and Real-world Evidence (CORE)
2000 Galloping Hill Road, Kenilworth, NJ 07033 Mailstop K-152F 211
Email: ravinder.dhawan@merck.com
Tel: 908-930-8970

References

- 1 de Wit R, Kulkarni GS, Uchio EM, et al. Health-related quality of life and updated follow-up from KEYNOTE-057: phase 2 study of pembrolizumab for patients with high-risk non-muscle-invasive bladder cancer unresponsive to Bacillus Calmette-Guérin. Poster presented at ESMO 2019 (European Society for Medical Oncology); September 27-October 1, 2019; Barcelona, Spain
- 2 Presentation at the Oncologic Drugs Advisory Committee (ODAC) Meeting, December 17, 2019. <https://www.fda.gov/media/133956/download>
- 3 BCG-Unresponsive Nonmuscle Invasive Bladder Cancer: Developing Drugs and Biologics for Treatment Guidance for Industry. U.S. Department of Health and Human Services Food and Drug Administration, 2018
- 4 Steinberg RL, Thomas LJ, Brooks N, et al. Multi-Institution Evaluation of Sequential Gemcitabine and Docetaxel as Rescue Therapy for Nonmuscle Invasive Bladder Cancer. *J Urol.* 2020;203(5):902-909.
- 5 Milbar N, Kates M, Chappidi MR, et al. Oncological Outcomes of Sequential Intravesical Gemcitabine and Docetaxel in Patients with Non-Muscle Invasive Bladder Cancer. *Bladder Cancer.* 2017;3(4):293-303.
- 6 Dickstein R, Wu N, Cowan B, et al. VISTA, phase 3 trial of Vicinium, an EpCAM-targeted Pseudomonas exotoxin, in BCG-unresponsive non-muscle invasive bladder cancer. Global Congress on Bladder Cancer 2018, Madrid, Spain (2018)

Appendix Tables

Table 1: Transition probabilities from NMIBC to MIBC for pembrolizumab

Recommended: Using pembrolizumab PFS data + CR with DOR KM approach*	
12-month PFS	96.9% [1]
12-month CR	23.1%*
3-month TP (calculated)	1.36%

Keys: CR, complete response; DOR, duration of response; NMIBC, non-muscle invasive bladder cancer; MIBC, muscle invasive bladder cancer; TP, transition probabilities; PFS, progression-free survival

*Recommend approach (using CR with DOR KM, see Section 2 in the letter and Table 2 immediately below) yields 12-month CR of 23.1% (=40.6%*56.8%), based on 3-month initial CR of 40.6% and 12-month DOR of 56.8% since initial treatment.

Table 2: Transition probabilities from CR to NMIBC for pembrolizumab

Recommended: Using DOR KM estimates to address censoring				
Month (from initial treatment)	DOR KM *	TP ^a (Base Case: using median and exponential function to smooth out the KM curve)	TP ^b (Scenario 1: using DOR KM each 3-month data to calculate time-varying TP)	TP ^c (Scenario 2: using DOR KM 3-month and 24-month data to calculate time constant TP)
0	n/a	n/a	n/a	n/a
3	100.0%	n/a	n/a	n/a
6	100.0%	0.1205	0.0000	0.1136
9	78.0%	0.1205	0.2200	0.1136
12	56.8%	0.1205	0.2718	0.1136
>12	43.0% (at 24 mo)	0.1205	0.1136	0.1136

Keys: CR, complete response; DOR, duration of response; NMIBC, non-muscle invasive bladder cancer; n/a, no applicable; mo, month; TP, transition probabilities

* Digitized from DOR KM curve [2]. Note that month 3 in this table equals to month 0 in DOR KM curve (Appendix Figure 2).

^a TPs were calculated based on median DOR (16.2 months): $1 - e^{(-\ln(2)/16.2*3)} = 0.1205$

^b TPs were calculated based on the DOR KM % at 3, 6, 9, 12 and 24 months and are time varying. E.g., TP at month 12 = $1 - 56.8\% / 78.0\% = 0.2718$. The TPs beyond 12 months are assumed to be the same rate as that between month 3 and month 24: $1 - e^{(\ln(1 - (1 - 43\%/100\%))/(24 - 3)*3)} = 0.1136$.

^c TPs were assumed to be the same rate as that between month 3 and month 24: $1 - e^{(\ln(1 - (1 - 43\%/100\%))/(24 - 3)*3)} = 0.1136$.

Please note that all scenarios using KM estimates to calculate TPs produce similar model results, suggesting the robustness of the base case approach of using median DOR and exponential function to smooth out the curve.

Table 3: Model predicted undiscounted LYs in each health state and mDOR

	Model predicted LYs in each health state *							Model predicted mDOR #
	Initial	CR	NMIBC	MIBC	Metastasis	Post-Cystectomy	Total	
Gem ± Doc	0.25	4.85	2.72	0.11	0.85	1.95	10.73	45 mo
Pembrolizumab (ICER's approach)	0.25	0.52	3.04	0.12	0.97	2.19	7.09	12 mo

Keys: CR, complete response; Doc, docetaxel; Gem, gemcitabine; NMIBC, non-muscle invasive bladder cancer; MIBC, muscle invasive bladder cancer; mDOR, median duration of response; mo, months

*As an example, model predicted accumulated LYs in CR=SUM(R5:R106)*0.25 for gem±doc, from the ICER model Gem+Doc (cis) tab.

Model predicted mDOR = the number of months that has elapses when around 50% of initial CR patients remain in CR, since the initial CR (at month 3 of the trial). For pembrolizumab, at month 48 (cell B21), 36% (=72%*0.5, cell R21) of patients remain in CR vs the initial CR 72% (cell R6) at month 3 (cell B6), so model predicted mDOR=48-3=45 months for Gem+Doc, from the ICER model Gem+Doc (cis) tab.

Validity check: Based on the ICER model, it is estimated that, on average, Gem+Doc patients remain in CR for 4.85 years, and the mDOR is 45 months. These estimates contradict with clinical insight and other published data (suggesting lower efficacy) [5]. In contrast, the predicted average LY in CR is only 0.52 years for pembrolizumab. In addition, the model-predicted mDOR for pembrolizumab is 12 months, much lower than the mDOR (16.2 months) from KEYNOTE-057. These predictions are questionable.

Table 4: Transition probabilities from CR to NMIBC for oportuzumab monatox

Month	HGRFS approach (current)		CR approach (alternative)	
	HGRFS	TP *	CR	TP (calculated)#
3	42%	n/a	40%	n/a
6	32%	23.8%	28%	30.0%
9	22%	31.3%	21%	25.0%
12	20%	9.1%	17%	19.0%
>12	13% &	15.4%	n/a	24.8%

& Percentage at 24 months

* The transition probabilities were reported from ICER report, except that 23.8% replaces the incorrect number (20%) in the report.

TPs were calculated based on the CR at 3, 6, 9 and 12 months and are time varying. E.g., TP at month 6=1-28%/40%=30%. The TPs beyond 12 months are assumed to be the same rate as that between month 3 and month 12: $1 - e^{(\ln(1 - (1 - 17\%/40\%)) / (12 - 3) * 3)} = 24.8\%$.

Please note that the two approaches generate quite different transition probabilities over time which have considerable impacts on the model results.

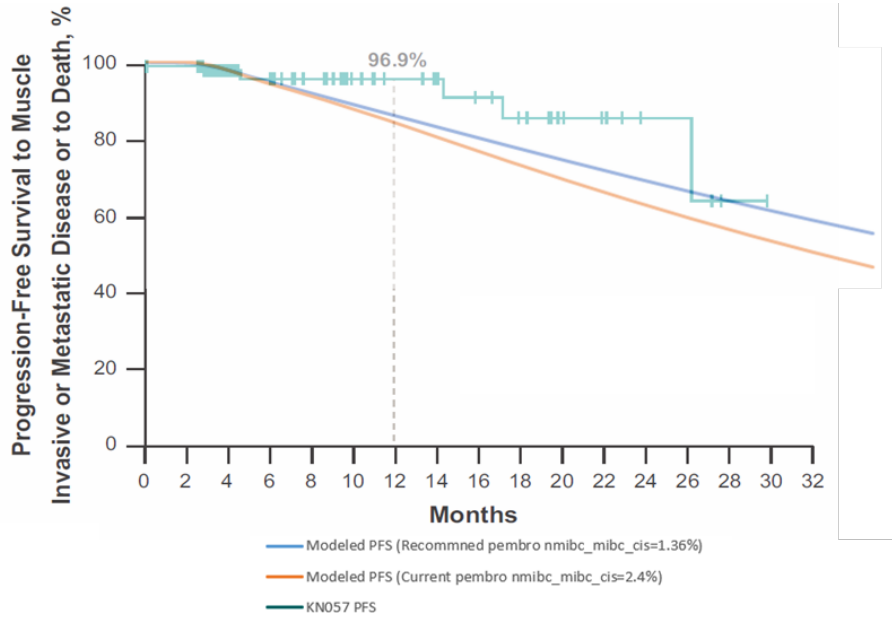
Table 5: Gemcitabine with and without docetaxel in CIS: errors and corrections

	Errors	Correction	Calculation	Note
RR	0.8	0.77	Calculated from the mean 12-month HGPFS from Daniels 2020 (53%), Steinberg 2015 (46%), and Milbar 2017 (51%) divided by Steinberg 2020 (65%). Data are from ICER report table 4.14.	Suggest to use RR=0.66 based on the mean 24-month HGRFS from Daniels 2020 (35%) and Milbar 2017 (34%) divided by Steinberg 2020 (52%), if a lower RR is preferred.
TP from CR to NMIBC > 12m	0.026	0.045	In the model input excel, tab "Probs_gem_cis", cell L9 should be 1, instead of 1.75, based on 12-month HGRFS (0.6) and 24-month HGRFS (0.5).	Suggest to use TP of $1 - e^{(\ln(1 - 0.5/0.9))/(24-3)*3)} = 0.081$, calculated from 3-month HGRFS (0.9) and 24-month HGRFS (0.5) to be consistent with the approach for other treatments

Keys: CR, complete response; HGRFS, high-grade recurrence free survival; NMIBC, non-muscle invasive bladder cancer; RR, rate ratio; TP, transition probabilities

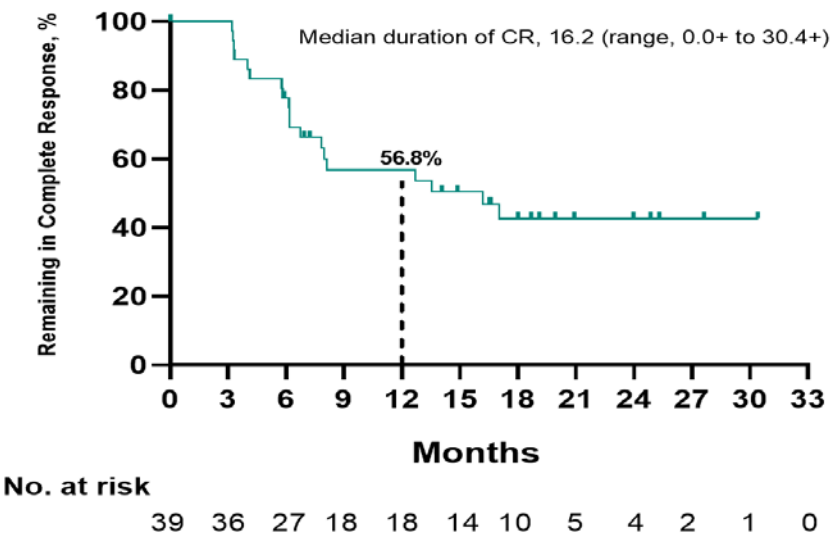
Appendix Figures

Figure 1: PFS from KN057 [1] and PFS predicted from the economic model *



* As an example, model predicted PFS at month 3=SUM(Q6:S6) from the ICER model pembrolizumab (cis) tab.

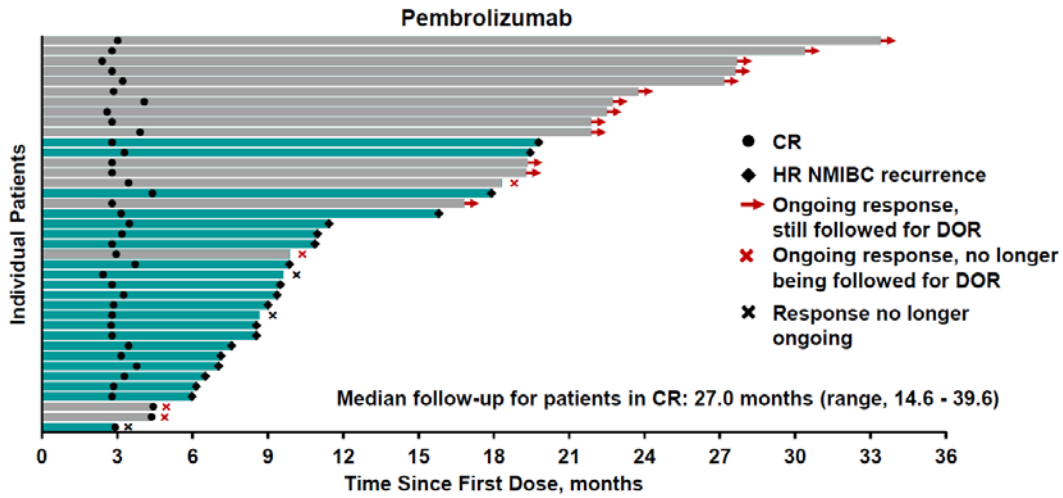
Figure 2: Duration of response for patients who achieved CR at first evaluable time point* for pembrolizumab [2]



*Month 0 (i.e., when initial CR was achieved) = month 3 from treatment initiation

When the number of patients in CR (i.e., number at risk) reduces over time, it can be due to either an event (loss of CR, represented by the drop in KM curve) or a censor (e.g., reach the end of study cutoff, start new treatments, or have non-evaluable assessments). The censored cases were detailed in Figure 3. Please note that, in Figure 2, duration of response was calculated from initial CR, whereas, in Figure 3, time zero represents the start of the trial.

Figure 3: Plot of Time to Complete Response and Time to Recurrence or Progression [2]



Month 0 = time point of first dose.

Censored subjects (indicated by red arrow, red cross, and black cross) include all complete responders who have non-evaluable assessments, start new anti-cancer treatment, are lost to follow-up, or have ongoing response who are alive, have not progressed, have not started new anti-cancer treatment, are not lost to follow-up.

Please note that, in Figure 2, duration of response was calculated from the initial CR, whereas, in Figure 3, time zero represents the start of the trial.



October 15, 2020

Steven D. Pearson, MD, MSc, FRCP
President
Institute for Clinical and Economic Review
One State Street, Suite 1050
Boston, MA 02109 USA

RE: Draft Evidence Report “Nadofaragene Firadenovec and Oportuzumab Monatox for BCG-Unresponsive, Non-Muscle Invasive Bladder Cancer”

Dear Dr. Pearson:

Patients Rising Now advocates on behalf of patients with serious and chronic conditions and diseases for them to have access to life-improving and life-saving therapies and services. Access to such treatments and services is essential, and it spans affordability, insurance coverage and physical access. To support improved access, we are committed to engaging patients, caregivers, physicians, media, health policy experts, payers, providers, and others to foster people-centered discussions about the entire U.S. health care system. That is, our goal is a balanced dialogue that illuminates the truth about health care innovations and advancements in a just and equitable way.

We appreciate the opportunity to provide our comments on ICER’s September 17th Draft Evidence Report “Nadofaragene Firadenovec and Oportuzumab Monatox for BCG-Unresponsive, Non-Muscle Invasive Bladder Cancer.” Our comments about the draft report are organized below into sections about People-Centered Perspectives; Diagnostic and Treatment Complexities and Opportunities; Uncertainties and Assumptions; and Additional Points.

People-Centered Perspectives

As is well known, people with cancer face a variety of health care and life concerns; being diagnosed with cancer can be a very distressing and jarring event. The draft report describes this at the onset: “Bladder cancer can have a large effect on patients’ lives, particularly if the cancer does not respond adequately to standard therapy.”ⁱ While the patient perspectives discussed in Section 2 are useful, they seem to be only derived from “two patient advocacy groups and a patient treated for bladder cancer.”ⁱⁱ ICER should have engaged with as broad an array of patients as possible. Although the patient advocacy groups may have provided access to more patient insights, the draft report does not include that level of specificity about the input ICER received.

Other important – and specific – patient perspectives are stated in the draft report:

- “Patients and patient advocacy groups highlighted the deficiencies of currently available treatments for patients with BCG-unresponsive NIMBC.”ⁱⁱⁱ
- “[M]aintenance 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.”^{iv}

- “[B]ladder 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.”^v
- “The impact of NMIBC on patients and their caregivers include[s] disruption of personal and professional lives due to treatment, resulting in decreased work productivity and earning potential.”^{vi}
- “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.”^{vii}

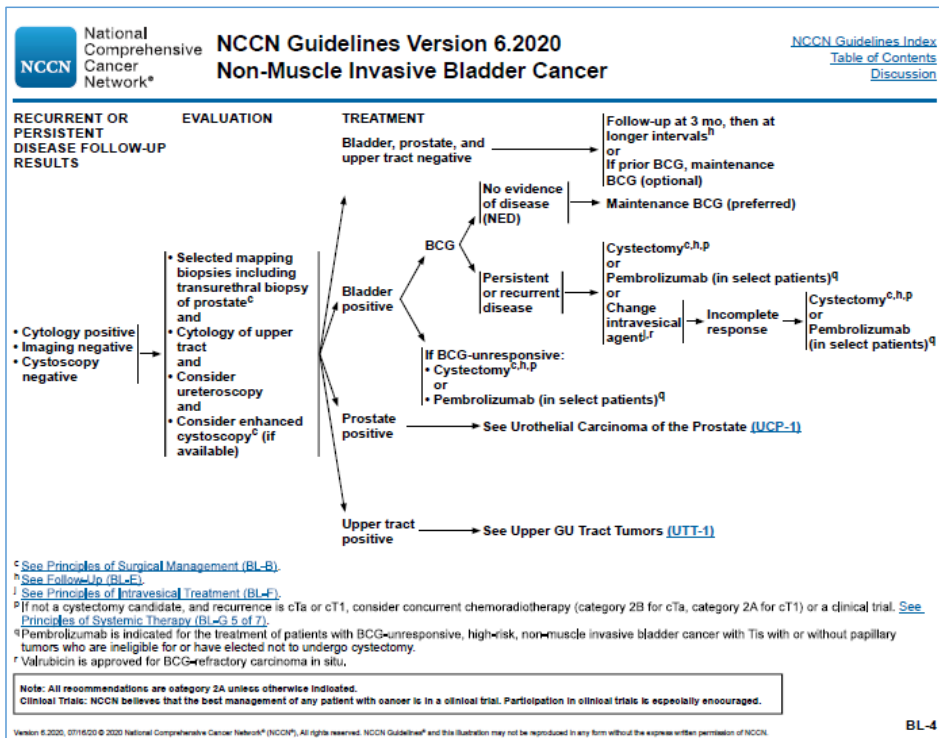
Diagnostic and Treatment Complexities and Opportunities

Cancer is widely recognized to be a category of disease rather than a single disease. Different cancers present very different concerns and challenges for patients. For example, glioblastoma is very hard to treat and most people live only a few years; squamous cell skin cancer is very common and easily treated or cured (if it hasn’t spread too widely); and prostate cancers have varying degrees of severity and aggressiveness. We point this out since not only do different cancers represent different clinical outlooks and life choices for patients, but as biomedical science has advanced, it is clear that even a single “type” of cancer is really an amalgam of many different subtypes – often characterized by specific genomic and biomarkers or mutations. Perhaps the best example of that variation is breast cancer.^{viii}

Commented [A1]: I don't see how that's relevant – if I am missing something, please overrule me.

In contrast, the treatment of bladder cancer is currently guided by its clinical and pathological presentation, including traditional pathology markers of cellular changes, organ penetration, and spread.^{ix} This situation for bladder cancer is important because researchers hope and expect that genetic markers for characterizing bladder cancer will be discovered and validated, and targeted therapies will then be developed. However, increased barriers to accessing treatment, insurance coverage, or reimbursement would slow down those advances, ultimately harming the care for people who develop bladder cancer in the future, and thus society as a whole.

The diagnostic determinations for people who currently have bladder cancer are critical for guiding appropriate care choices – as is well illustrated from just one diagram in the NCCN’s 118-page July 2020 “Clinical Practice Guidelines in Oncology” for Bladder Cancer reproduced below. This diagram is relevant because it conveys the complex clinical decisions that people with bladder cancer must make with their clinicians to determine the treatment options and care plan that are best for them. That shared decision-making process is critical to ensure the patient receives the most appropriate treatment for himself or herself.



Uncertainties and Assumptions

The draft report summarizes – and attempts to analyze – the clinical trial data for two experimental treatments. The draft report states that the “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.” However, the draft report then indicates *it was not possible to conduct such direct comparisons*, and the entire review was done via modeling with significant uncertainty in the assumptions, making it hard to see the value of the conclusions.

The extent of the limited and problematic data underlying the draft report’s “analysis” is stated in the draft report itself:

“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.”^x

Additional examples of the abundant assumptions and presumptions based on extremely limited and uncertain data used in the draft report's modeling and attempts at forced analysis include:

- “We did not identify any studies directly comparing nadofaragene firadenovec to oportuzumab monatox or to any of the comparators.”^{xi}
- “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.”^{xii}
- “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.”^{xiii}
- “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.”^{xiv}
- “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.”^{xv}
- “The comparator for all treatments was usual care. For both NMIBC subgroups, usual care was intentionally left undefined.”^{xvi}
- “[O]nly 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.”^{xvii}
- “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.”^{xviii}
- For gemcitabine (an older medicine that is now available in generic form from multiple companies), the data was suboptimal, e.g., “outcomes stratified by tumor grade subgroups were generally not available and are presented in aggregate.”^{xix} And complete response data for gemcitabine with docetaxel “was not reported in any of the identified studies of gemcitabine with docetaxel.”^{xx}
- “The effectiveness of gemcitabine ± docetaxel was obtained from a large multicenter noncomparative retrospective evaluation. 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.”^{xxi}
- “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.”^{xxii}
- “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.”^{xxiii}
- **“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” (emphasis added).**^{xxiv}

We also note that there have been recent reports about pembrolizumab indicating that it may not be as effective as previously thought for treating bladder cancer.^{xxv} Since receiving FDA approval in 2017 for use in bladder cancer, pembrolizumab has had its approved label for bladder cancer modified several times. This is important not only for the treatment of individuals with bladder cancer, but it points out – once again – the ever-evolving nature of biomedical

science and best practices for clinical care. It is one reason why the NCCN updates its guidelines so frequently, and why ICER’s process of doing reviews before there is sufficient data, and cross-compound comparisons without actual data is dangerous – particularly when ICER is reticent to update its own work when new data is available.

Additional Points

- The application for nadofaragene firadenovec received a complete response letter from the FDA in May 2020 concerning some manufacturing issues,^{xxvi} so it is unclear when this treatment will be available for patients. And for oportuzumab monatox, according to the company, it is “on track to complete the BLA submission in the fourth quarter of 2020 and anticipates potential approval in mid-2021.”^{xxvii} Both those points of information should be included in the report.
- While Section 3 correctly notes that neither of the two agents have been approved by the FDA, we did find a preliminary clinical use policy from national carrier Centene from February 2020, which stated its policy would be effective upon the date of FDA approval and that its use criteria “will mirror the clinical information from the prescribing information once FDA-approved.”^{xxviii} We point this out to indicate that health insurance companies – in this case one that provides commercial as well as Medicaid plans – are thinking ahead and preparing for coverage decisions about new treatments prior to FDA approval. Clearly, they are doing this using their internal review and evaluation processes, and not relying on ICER to do this for them. As we’ve repeatedly pointed out, doing that makes sense since they need to determine what is appropriate for the population of people for whom they are providing health insurance, rather than some generalized assessment about the “cost-effectiveness of different care pathways for broad groups of patients.”^{xxix}

Conclusions

Patients Rising Now is pleased that people with bladder cancer may soon have new and better treatment options. While the draft report presents information about the serious consequences of bladder cancer for patients and their caregivers – and the benefits of treatment options that may require fewer treatments or travel – ICER once again minimizes or ignores those implications and presents a very un-people-centered assessment.

Therefore, we are concerned that based on the very limited data available for this review, access to current and future treatments for bladder cancer may be limited by insurance plans through formulary, cost-sharing, or prior authorization schemes based on ICER’s activities, which may at the same time expand administrative burdens for clinicians and patients.

Sincerely,



Terry Wilcox
Co-Founder & Executive Director, Patients Rising Now

ⁱ Draft Report p 1

ⁱⁱ Draft Report p 8

ⁱⁱⁱ Draft Report p 8

-
- iv Draft Report p 8
- v Draft Report p 9
- vi Draft Report p 53
- vii Draft Report p 39
- viii <https://www.uptodate.com/contents/breast-cancer-guide-to-diagnosis-and-treatment-beyond-the-basics>
- ix “Are Molecular Markers for Bladder Cancer Ready for Prime Time?” December 18, 2019, <https://dailynews.ascopubs.org/doi/10.1200/ADN.19.190486/full/>
- x Draft Report p 36
- xi Draft Report p 15 and p 19
- xii Draft Report p 14
- xiii Draft Report p 36
- xiv Draft Report p 55
- xv Draft Report p 41
- xvi Draft Report p 42
- xvii Draft Report p 14
- xviii Draft Report p 19
- xix Draft Report p 26
- xx Draft Report p 33
- xxi Draft Report p 46
- xxii Draft Report p 50
- xxiii Draft Report p 67
- xxiv Draft Report p 68
- xxv <https://www.fiercepharma.com/marketing/merck-s-keytruda-flops-bladder-cancer-trial-giving-roche-s-tecentriq-a-chance-at-bigger>
- xxvi <https://www.cantechletter.com/2020/09/thermalase-is-a-high-risk-high-reward-play-says-mackie-research/>
- xxvii Sesen Bio press release, August 10, 2020, <https://ir.sesenbio.com/news-releases/news-release-details/sesen-bio-reports-second-quarter-2020-financial-results-and>
- xxviii “Clinical Policy: Nadofaragene Firadenovec (Instiladrin)” from Centene Corporation, <https://www.coordinatedcarehealth.com/content/dam/centene/policies/pharmacy-policies/CP.PHAR.461%20Nadofaragene%20Firadenovec.pdf> (Accessed September 22, 2020)
- xxix Draft Report p iii

UNIVERSITY OF MINNESOTA

*Twin Cities Campus
College of Pharmacy*

*Graduate Program in Social &
Administrative Pharmacy*

*7-155 Weaver-Densford Hall
308 Harvard Street S.E.
Minneapolis, MN 55455*

**Dr S D Pearson
President
Institute for Clinical and Economic Review
Two Liberty Square, 9th Floor
BOSTON MA 02109**

13 October 2020

Submitted via Email

Email: publiccomments@icer-review.org

My dear Dr Pearson

PUBLIC COMMENT: DRAFT EVIDENCE REPORT

NADOFARAGENE FIRADENOVEC AND OPORTUZUMAB MONATOX FOR BCG-UNRESPONSIVE, NON-MUSCLE INVASIVE BLADDER CANCER: EFFECTIVENESS AND VALUE

Thank you for this valuable opportunity to comment on the Draft Evidence Report for Nadofaragene Firadenovec and Oportuzumab Monatox in bladder cancer ¹.

As you will no doubt recall, you are aware of my concerns that the ICER reference case framework for value assessment fails to meet the standards of normal science. That is, your reports lack credibility in the claims made for the value of products; they cannot be evaluated empirically nor can the claims be replicated. While you might view these reports and the application of lifetime incremental cost-per-QALY calculations and the application of cost-per-QALY thresholds as the state of the art in health technology assessment, the problem is that the entire exercise is essentially a waste of time. This is why I have coined the term impossible or I-QALY as you and many others insist in believing that ordinal utilities have multiplicative properties ².

This conclusion rests on the failure to recognize the limitations imposed by the axioms of fundamental measurement. You focus on constructing simulated QALY claims yet we know that the utility score (typically the EQ-5D-3L/5L) is an ordinal measure. It cannot support multiplication which is required

to transform modelled time spent in a disease state to its quality adjusted time equivalent. This means the I-QALY is a mathematically impossible construct. By extension, not only are lifetime incremental cost per I-QALY claims impossible, but the attempt to generate pricing recommendations (e.g., the notion of a 'fair price') through the application of nominal cost-per-I-QALY thresholds is similarly a waste of time. Hopefully manufacturers and health system decision makers will not take this effort seriously.

Unfortunately, the draft evidence report for bladder cancer, with the model developed by Professor Touchette and colleagues in the College of Pharmacy Modelling Group, University of Illinois at Chicago, also apparently believe (or at least they have an understanding) that the EQ-5D-3L utility scale has 'ratio' properties. There is no defense of this position or a proof for this belief. If ICER and the University of Illinois group wish to explore this further I would recommend a recent peer reviewed paper by myself and a colleague (note in particular the peer reviewers comments) ³. Perhaps the Illinois group could provide a proof that the EQ-5D has ratio properties (and even demonstrate that it has by default interval measurement properties).

You may recall that in the public comment window for ulcerative colitis, I raised a number of questions designed to establish the basis for your belief in the ratio scale property of the EQ-5D; specifically your ability to provide a proof of this claim. Your response to these questions indicated that you could not provide a proof. Your response reads:

*We (and most health economists) **have the understanding** (emphasis added) that the EQ-5D (and other multiattribute instruments) do have ratio properties. The EQ-5D value sets are based on time trade-off assessments (which are interval level) with preference weights assigned to different attributes. We fail to see why this should be considered as an ordinal (ranked) scale. ICER believes that the dead state represents a natural zero point on a scale of health related quality of life. Negative utility values on the EQ-5D scale represent states considered worse than dead.*

A detailed rebuttal of this rather strange and inconsistent response has been published strange response ⁴. Rather than repeat these comments (although it might be noted that the TTO does NOT have interval properties ⁵), ICER should be asked once again to provide a proof that the EQ-5D, which features in the bladder cancer report, has a ratio scale. It is somewhat self-defeating to maintain that the EQ-5D-3L has a natural zero and in the next sentence point out that EQ-5D can create negative utility values. ICER cannot have it both ways: a pseudo-ratio scale with negative utilities and a natural zero point? It is not clear what a natural zero point means. In the case of the EQ-5D-3L the zero is simply an artifact of the equation or algorithm that creates the utilities. Unlike, for example, a true zero in measuring weight (i.e., you can't have negative weights). If ICER or the academic group at the University of Illinois are not sure of this, they might refer you to the standard textbook on health technology assessment (Drummond et al. 4th Eds. pg. 148)⁶.

As detailed in a number of my publications, the I-QALY is an impossible construct which means, by extension, that your reference case value assessment framework is invalid ⁷. It is up to you, but I would think you should advise your audience in ICER subscribers and the various formulary assessment groups, and PBMs of these limitations on your imaginary modelled recommendations.

Yours sincerely

Paul C. Langley, Ph.D.
Adjunct Professor
College of Pharmacy
University of Minnesota
MINNEAPOLIS MN
Director
Maimon Research LLC
TUCSON AZ
Email: langley@maimonresearch.com
Website: www.maimonresearch.net

REFERENCES

-
- ¹ 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/>
- ² Langley P. The Great I-QALY Disaster. *InovPharm*. 2020;11(3): No 7 <https://pubs.lib.umn.edu/index.php/innovations/article/view/3359/2517>
<https://doi.org/10.24926/iip.v11i3.3359>
- ³ Langley PC and McKenna SP. Measurement, modeling and QALYs [version 1; peer reviewed] *F1000Research* 2020, 9:1048 <https://doi.org/10.12688/f1000research.25039.1>
- ⁴ Langley P. The Impossible QALY and the Denial of Fundamental Measurement: Rejecting the University of Washington Value Assessment of Targeted Immune Modulators (TIMS) in Ulcerative Colitis for the Institute for Clinical and Economic Review (ICER). *InovPharm*. 2020;11(2): No 17 <https://pubs.lib.umn.edu/index.php/innovations/article/view/3330/2533>
<https://doi.org/10.24926/iip.v11i3.3330>
- ⁵ Lugnér AK, Krabbe P. An overview of the time trade-off method: concept, foundation, and the evaluation of distorting factors in putting a value on health. *Exp Rev Pharmacoeconomics Outcomes Res*. 2020; 29(4):331-342
- ⁶ Drummond M, Sculpher M, Claxton K et al. Methods for the Economic Evaluation of Health Care Programmes. 4th Ed. New York: Oxford University Press, 2015
- ⁷ Langley P. Nonsense on Stilts – Part 1: The ICER 2020-2023 value assessment framework for constructing imaginary worlds. *InovPharm*. 2020;11(1): No. 12 <https://pubs.lib.umn.edu/index.php/innovations/article/view/2444/2348>

October 15, 2020

Dr. Steven D. Pearson
President
Institute for Clinical and Economic Review
Two Liberty Square, Ninth Floor
Boston, MA 02109

Dear Dr. Pearson,

The Partnership to Improve Patient Care (PIPC) appreciates this opportunity to comment on the Institute for Clinical and Economic Review's (ICER) draft evidence report regarding treatments for bladder cancer. Bladder cancer can present many challenges to a patient's quality of life, and there are currently very few treatment options for patients with high-risk non-muscle invasive bladder cancer that is unresponsive to BCG, so it is critical that new treatments are evaluated carefully when there is appropriate available evidence. PIPC asks ICER to consider the following comments as it moves forward with its assessment.

ICER continues to conduct studies prematurely

PIPC echoes the Cancer Support Community and other stakeholders in the belief that this report is being undertaken prematurely. ICER has chosen again, in the absence of sufficient evidence, to prematurely assess the value-based price of these drugs. No respected health technology assessment agency anywhere in the world evaluates new drugs before phase III data is available and the relevant drug regulation agency has approved its use. Despite this, ICER has made it common practice to prematurely assess the cost-effectiveness of drugs. Without a drug being approved and a price established, it is irresponsible to evaluate its cost-effectiveness.

PIPC has concerns about the sources and construction of ICER's health state utility inputs

The health state utility values for the model seem to be taken from a single study undertaken in the UK where quality of life data was collected as part of the BOXIT trial.¹ The approach taken in this study was to estimate utility loss increments, not to actually estimate utility values of certain health states. This method is a valuable way to capture variance in disease states and comorbidities, but it must be approached correctly.

The problem with ICER's use of these utility values is that these incremental utilities have been applied individually to create proxy health states for the ICER model. In reality, many of these utility loss increments will be relevant to most, if not all, patients, so the use of individual utility loss increments – rather than combinations of utility loss increments is likely to significantly overestimate the health utility levels of people in more severe states of disease. For example, in the ICER model, patients with inoperable advanced metastatic bladder cancer seem to have an

¹ Cox E, Saramago P, Kelly J, et al. Effects of Bladder Cancer on UK Healthcare Costs and Patient Health-Related Quality of Life: Evidence From the BOXIT Trial. *Clin Genitourin Cancer*. 2019.

HSUV of 0.7. This is a magnitude of quality life higher than people with arthritis², dermatitis³ or migraine.⁴ It is highly unlikely that this an accurate summation of quality of life for people suffering the late stages of incurable cancer, and further demonstrates the flawed logic of a QALY-based model. The result of this overestimation is that the value of reducing time spent in these health states – the stated goal of most new treatments for any disease – will be undervalued.

Mixed data sources for measures of effectiveness are likely to lead to biased estimates in the ICER model

ICER chooses to compare retrospective data to randomized clinical trial data in order to compare effectiveness across drugs. Whenever possible, ICER should compare equivalent data sets for consistency.

The review of the phase II and III trials shows a complete response (CR) for gemcitabine ± docetaxel of no greater than 39%, and HGFERS at 12 months ranging from 21-28% in populations with a high proportion of CIS ±HIG Ta/T1. Yet the ICER model uses a much higher figure that comes from a retrospective chart review of selected patients of 60-69%, and a figure of 75.2% for complete response. ICER acknowledges that these response rates are peculiarly high yet still chooses to use this data instead of comparable source data from trials.

Retrospective data is incredibly valuable when used correctly,⁵ but the issue here is that there are not equivalent data sets for new drugs or therapeutic approaches. There is strong empirical evidence that the relative effectiveness of new therapies tend to improve over time, as physicians and providers develop better understanding of when, to whom and how to incorporate therapies into everyday treatment plans.⁶ This learning-by-doing leads to a rise in effectiveness, as has been shown to exist in oncology for multiple tumors.⁷ Comparing efficacy rates from a phase II or III trial with a retrospective case review is not a reasonable comparison.

ICER uses the discriminatory Quality-Adjusted Life Year (QALY)

As PIPC has voiced many times in the past, we are concerned with ICER's continued use of the Quality-Adjusted Life Year (QALY). The QALY is known to discriminate by devaluing

² Van den Hout WB, Goekoop-Ruiterman YP, Allaart CF, De Vries-Bouwstra JK, M. Hazes JM, Kerstens PJ, Van Zeben D, Hulsmans HM, De Jonge-Bok JM, De Sonnaville PB, Dijkmans BA. Cost-utility analysis of treatment strategies in patients with recent-onset rheumatoid arthritis. *Arthritis Care & Research*. 2009 Mar 15;61(3):291-9.

³ Sonya Kahn MP. Economic evaluation of dupilumab for moderate-to-severe atopic dermatitis: a cost-utility analysis. *Journal of Drugs in Dermatology*. 2018 Jul;17(7):750-6.

⁴ Xu R, Insinga RP, Golden W, Hu XH. EuroQol (EQ-5D) health utility scores for patients with migraine. *Quality of life research*. 2011 May 1;20(4):601-8.

⁵ Bowrin K, Briere JB, Levy P, Millier A, Clay E, Toumi M. Cost-effectiveness analyses using real-world data: an overview of the literature. *Journal of medical economics*. 2019 Jun 3;22(6):545-53.

⁶ Gaynor M, Seider H, Vogt WB. The volume-outcome effect, scale economies, and learning-by-doing. *American Economic Review*. 2005 May;95(2):243-7.

⁷ Stevens W, Incerti D, et al. An empirical investigation of time-varying cost-effectiveness across the product life cycle. *Health Economics*. 2020 May;29(5):580-90.

treatments designed for individuals with disabilities and chronic illnesses. In a 2019 report, the National Council on Disability, an independent federal agency, found that use of the QALY is contrary to United States civil rights laws and due to its implications for disability discrimination.⁸ The report specifically focuses on the United Kingdom's use of the QALY, highlighting cancer patients' lack of access to novel treatments and worse outcomes. PIPC encourages ICER to abandon the use of the QALY for this assessment and all those moving forward.

Conclusion

PIPC has a strong interest in the evolution of patient-centric methods of value assessments so they serve as a usable tool for patients and providers in their decision making. We appreciate ICER's review of our comments on this assessment and are happy to offer further assistance if necessary.

Sincerely,



Tony Coelho

Chairman, Partnership to Improve Patient Care

⁸ National Council on Disability. (November 16, 2019). Quality-Adjusted Life Years and the Devaluation of Life with Disability. https://ncd.gov/sites/default/files/NCD_Quality_Adjusted_Life_Report_508.pdf.



October 15th, 2020

Sesen Bio appreciates the opportunity to comment on ICER's draft evidence report and voting questions on Nadofaragene Firadenovec and Oportuzumab Monatox for BCG-unresponsive, non-muscle invasive bladder cancer.

Our main recommendations on the draft report are summarized here:

- 1) The gemcitabine plus docetaxel data presented in the report was generated from retrospective studies and extreme caution should be taken regarding the outcomes.
- 2) Pembrolizumab Phase 2 trial enrolled 62.5% of OUS patients.
- 3) The lifetime total cost of usual care was estimated at \$190,000 by ICER. However, there is no reference provided for this figure and corresponds to a hypothetical usual care. The reported cost-effectives per QALY are premature.
- 4) As outlined in the FDA guidance, avoiding cystectomy is a key secondary endpoint for NMIBC therapies and Sesen Bio believes that the report should further discuss this point.

Detailed comments:

1) The gemcitabine plus docetaxel data presented in the report was generated from retrospective studies and extreme caution should be taken regarding the outcomes.

All the studies evaluating gemcitabine have been performed prior to the 2018 FDA definition of BCG-unresponsive patients hence the data is not comparable to that of the Oportuzumab monatox Phase 3 trial. The gemcitabine/docetaxel combination studies published by Steinberg et al., 2015 and Milbar et al., 2017 contained heterogenous patient populations comprised of BCG-unresponsive, BCG naïve or BCG intolerant patients and low-grade patients. The patient population in the Daniels et al., 2020 paper is defined as BCG-failure and not characterized as BCG-unresponsive. Therefore, the data from these three studies was generated with an easier patient population to treat compared to Nadofaragene Firadenovec, Pembrolizumab and Oportuzumab monatox. We believe that the data can not be used for direct comparison with Oportuzumab monatox, Nadofaragene Firadenovec and Pembrolizumab.

The only suitable comparator data is from the paper published by Steinberg et al., 2020 in which a cohort of 71 CIS and 34 PAP patients are defined as BCG-unresponsive. However, despite intriguing data, the following citations from the paper "limitations include the retrospective nature and moderate follow-up" and "might be influenced by selection bias given that physician discretion was utilized to determine those who received treatment" clearly indicate that the data should be interpreted with extreme caution. Moreover, the comparison with Oportuzumab monatox data is difficult since the number of prior BCG cycles and the proportion of BCG-unresponsive CIS patients with Ta or T1 papillary disease are not indicated. As mentioned in the ICER report, the difference in the number of prior BCG cycles and proportion of patients with CIS + T1 disease does not allow comparison between trials (page 36).



All together, given the retrospective nature of the studies, the heterogeneity of the patient population and the presence of low-grade patients, the gemcitabine docetaxel data presented in the report may not represent the outcomes of a clinical trial enrolling only BCG-unresponsive patients. An appropriate clinical trial should be performed to assess the efficacy and safety of gemcitabine/docetaxel combination as per 2018 FDA guidance. Of note, a meta-analysis performed by Merck showed that the historical rate at 3 months for BCG-unresponsive CIS patients treated with a single chemotherapeutic agent was 21% (CI 95%: 15, 27%) (5). Sesen Bio believes that the data from single chemotherapeutic agents should be used for comparison since Oportuzumab monatox was used as a monotherapy.

Sesen Bio agrees with ICER that the evidence rating is insufficient to compare gemcitabine/docetaxel with Oportuzumab monatox. For this reason, Sesen Bio would like to ask ICER to remove question 5 from the voting list.

2) Pembrolizumab Phase 2 trial enrolled 62.5% of OUS patients.

The report should mention that out of 96 patients evaluated after Pembrolizumab treatment, 62.5% (60 of 96) of patients were enrolled outside of the US and only 37.5% (36 of 96) in the US. The CR rate for the OUS cohort was 47% vs. 30.6% for the US cohort (page 24 of the briefing book) (5). The report should also specify that the median duration of response was 16.2 months for all patients, however there is no data specifically for the US cohort.

Sesen Bio agrees with ICER that the evidence rating is insufficient to compare Pembrolizumab with Oportuzumab monatox. But more importantly, since most of the data for the US cohort is unknown, Sesen Bio would like to suggest that ICER removes question 7 from the voting list.

3) The lifetime total cost of usual care was estimated at \$190,000 by ICER. However, there is no reference provided for this figure and corresponds to a hypothetical usual care. The reported cost-effectives per QALY are premature.

Without a reference, Sesen Bio cannot comment on the lifetime total cost of usual care estimated at approximately \$190,000 for CIS and papillary patients by ICER. This number is lower than the cumulative cost of care over a 5-year period of \$366,143 for high-risk NMIBC published by Mossanen et al., 2019. Furthermore, the article reported that the primary driver of cost was progression to MICB contributing to 92% of the overall cost for high-risk disease. Therefore, Sesen Bio believes that the long-term data of the trial will increase the cost-effectiveness of Oportuzumab monatox.

As the data matures, Sesen Bio is convinced that Oportuzumab monatox will be recognized as a viable alternative to cystectomy by urologists as a cost-effective alternative by payers. Based on multiple rounds of market research, payers view Oportuzumab monatox as cost effective, specifically due to outcome data such as time to cystectomy, overall survival and progression-free survival, as well as the favorable safety profile.



4) As outlined in the FDA guidance, avoiding cystectomy is a key secondary endpoint for NMIBC therapies and Sesen Bio believes that the report should further discuss this point.

The 2018 FDA guidelines indicates that “the goal of therapy in patients with BCG-unresponsive NMIBC is to avoid cystectomy” (7). Radical cystectomy not only has a tremendous impact on the quality of life for a patient, including catheterization and urinary diversion, but it also comes with significant costs to the healthcare system. From the data in our Phase 3 trial, 76% of patients treated with Oportuzumab monatox are estimated to remain cystectomy-free for 3 years. Additionally, responders have a statistically significantly higher probability of remaining cystectomy-free at 2 years than non-responders (88% vs. 61%), which could change the lives of patients and provide significant savings for the healthcare system.

The Pembrolizumab Phase 2 study only enrolled patients who were ineligible or refused to have a cystectomy. As a consequence, cystectomy data was not included as a secondary endpoint. Therefore, Pembrolizumab is only approved for “the treatment of patients with Bacillus Calmette-Guerin (BCG)-unresponsive, high-risk, non-muscle invasive bladder cancer (NMIBC) with carcinoma in situ (CIS) with or without papillary tumors who are **ineligible for or have elected not to undergo cystectomy**”. Sesen Bio believes that any cystectomy data from the Phase 2 trial should be taken with caution since a selection bias may have been introduced by enrolling a population in which 95% of patients refused to have a cystectomy (ODAC, FDA presentation, slide 19) (8).

As BCG-unresponsive patients are facing a difficult decision with lifetime implications on quality of life, Sesen Bio believes that the cystectomy data obtained with Oportuzumab monatox will be a differentiating factor from other intravesical or systemic therapies.

Minor comments:

1) Reporting of the adverse events (AEs): The data reported for Nadofaragene firadenovec are treatment-related adverse events (TRAEs) (Table 4.3, page 19); therefore, table D5 should be edited accordingly. However, all treatment-emergent adverse events regardless of causality are reported for Oportuzumab monatox (Table 4.6, page 22). For consistency and fair comparison, Sesen Bio recommends that ICER reports either all AEs or TRAEs for both products.

2) Progression to MIBC for the gemcitabine/docetaxel combination study (Steinberg et al. 2020): The report should clarify that it was 4% of patients from the entire patient population that progressed to MIBC i.e. 276 patients ($11/276 = 4\%$) (page 33). This number is misleading and does not exclusively represent the percentage of the BCG-unresponsive patients that progressed to MIBC.

3) Table 5.8, page 52: Using \$164,337, the net price per dose provided for Oportuzumab monatox in the table implies 55 to 60 doses per year which is not correct. Patients will receive up to 36 doses in the first year (12 doses from Week 1-6, 6 doses from Week 6-12 and 18 doses from Week 14-52) and up to 24 doses in the second year.



4) Figure 5.3, page 60: Replace Nadofaragene firadenovec with Oportuzumab monatox in some of the probability listings.

References:

1. Steinberg R, Thomas L, O'Donnell M et al. Sequential intravesical gemcitabine and docetaxel for the salvage treatment of non-muscle invasive bladder cancer: PROTOCOL. *Bladder cancer* 2015;1:65-72
2. Milbar N, Kates M, Chappidi MR et al. Oncological outcomes of sequential intravesical gemcitabine and docetaxel in patients of non-muscle invasive bladder cancer. *Bladder cancer*. 2017;3(4):293-303
3. Daniels MJ, Barry E, Milbar N et al. An evaluation of monthly maintenance therapy among patients receiving intravesical combination gemcitabine/docetaxel for nonmuscle-invasive bladder cancer. *Urologic oncology: Seminars and original investigations*. 2020;38(2):40e17-40e24
4. Steinberg RL, Thomas LJ, Brooks N et al. Multi-institution evaluation of sequential gemcitabine and docetaxel as rescue therapy for nonmuscle invasive bladder cancer. *Journal of urology*. 2020;203(5):902-909
5. Combined FDA and applicant ODAC briefing document for Pembrolizumab for high-risk non-muscle invasive bladder cancer. December 2019
6. 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 journal of urology*. 2019;37(10):2059-2065
7. BCG-Unresponsive Nonmuscle Invasive Bladder Cancer: Developing Drugs and Biologics for Treatment Guidance for Industry, FDA, February 2018
8. <https://www.fda.gov/media/133901/download>