CADTH REIMBURSEMENT REVIEW

Patient and Clinician Group Input

belzutifan (Welireg)

(Merck Canada Inc.)

Indication: WELIREG® is indicated for the treatment of adult patients with advanced renal cell carcinoma (RCC) following a programmed death receptor-1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitor and a vascular endothelial growth factor tyrosine kinase inhibitor (VEGF-TKI).

December 6, 2024

This document compiles the input submitted by patient groups and clinician groups for the file under review. The information is used by CADTH in all phases of the review, including the appraisal of evidence and interpretation of the results. The input submitted for each review is also included in the briefing materials that are sent to expert committee members prior to committee meetings.

Disclaimer: The views expressed in this submission are those of the submitting organization or individual. As such, they are independent of CADTH and do not necessarily represent or reflect the views of CADTH. No endorsement by CADTH is intended or should be inferred.

By filing with CADTH, the submitting organization or individual agrees to the full disclosure of the information. CADTH does not edit the content of the submissions received.

CADTH does use reasonable care to prevent disclosure of personal information in posted material; however, it is ultimately the submitter's responsibility to ensure no identifying personal information or personal health information is included in the submission. The name of the submitting group and all conflicts of interest information from individuals who contributed to the content are included in the posted submission.

CADTH

Patient Input Template for CADTH Reimbursement Reviews

Name of Drug: Belzutifan
Indication: for the treatment of adult patients with advanced renal cell carcinoma (RCC) following a programmed death receptor-1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitor and a vascular endothelial growth factor tyrosine kinase inhibitor (VEGF-TKI).
Name of Patient Group: Kidney Cancer Canada (KCC)
Author of Submission: Christine Collins, Executive Director, KCC

1. About Your Patient Group

Kidney Cancer Canada is a national community of patients, caregivers and health professionals who work to provide every Canadian touched by kidney cancer with support, education and advocacy for their care pathways and treatment options.

www.kidneycancercanada.ca

2. Information Gathering

In 2022 Kidney Cancer Canada, helped design and promote an international online survey of patients and caregivers in affiliation with the International Kidney Cancer Coalition (IKCC). This survey included over 2,213 respondents (patients and caregivers) from 39 countries sharing their experiences and insights. Canada had 139 respondents of which 111 (80%) were patients diagnosed with kidney cancer, and 28 (20%) were caregivers to someone who has been diagnosed with kidney cancer. The survey was designed to explore and benchmark worldwide patient experience in:

- Patient knowledge, expectations of treatment and shared decision making
- Clinical trials, research awareness and sources of information
- Quality of life and overall health status of respondents

The IKCC 2022 Patient Survey Global Report and the Canada report is available here:
https://ikcc.org/global-patient-survey/2022-global-patient-survey/

Further, Kidney Cancer Canada identified patients who had experience with belzutifan for the treatment of renal cell carcinoma by i) requesting that Canadian physician investigators who had patients enrolled in the LITESPARK-005 trial to provide these patients with a survey from KCC. KCC included a request (within the survey) for patients with belzutifan experience to consent to a live telephone interview.

Three patients with experience with belzutifan were identified through these efforts. Two of these patients consented to a telephone interview.

This report reflects the results of the IKCC survey, KCC's survey of patients and caregivers, and our one-on-one interviews with patients and caregivers with experience with the treatment under review. This submission is also informed by intelligence and insights Kidney Cancer Canada has garnered from more than 15 years of experience in patient support, research and advocacy in Canada related to kidney cancer.

3. Disease Experience

The Canadian Cancer Society (CCS) estimates there are 6,600 new cases of kidney cancer diagnosed in Canada each year. It is the sixth most common cancer in men and the eleventh most common cancer in women. Of the 6,600 Canadians diagnosed annually with kidney cancer, approximately 25% will be diagnosed as stage IV. Metastatic renal cell carcinoma (mRCC) is a fatal disease with no known cure. For patients with stage IV disease, the survival rate is poor with less than 10% of these patients surviving for 5 years or longer.

The majority of patients (65%) with RCC have localized disease when they receive their diagnosis. When the disease is confined to the kidney, surgery to remove the cancer, either through nephrectomy or partial nephrectomy is the standard of care. While variations in retrospective data collection complicate the ability to accurately estimate the number of patients who may experience disease recurrence after surgery, most models put the risk of recurrence at between 40% and 50%. Nonetheless, a very large proportion of patients will eventually have disease recurrence leading to a substantially shortened life expectancy.

While kidney cancer survival has significantly improved over the last dozen years because of new innovative treatments and improved access to those treatments, there remain unmet treatment needs in the metastatic setting. Specifically, there is an increasing number of patients lacking treatment options after progressing on existing lines of therapy.

4. Experiences With Currently Available Treatments

While tremendous advancements have been made in drug treatments for advanced RCC, different patients can have different responses to the same drug. In previous surveys we have discovered that about one quarter of patients report that their current treatments difficult to tolerate.

It is clear that patients require drug options that are less toxic. When assessing the value of a new drug, the importance overall of treatment choice and patient preference must be recognized, and, for patients who find a specific prescribed drug intolerable, treatment alternatives within that line of therapy are extremely important.

From the 2022 IKCC 2020 Patient Survey Canada report

<u>Barriers to treatment</u>

63% of respondents (n=79) reported experiencing no barriers to treatment, relative to 46% globally (n=953)

The most commonly experienced barriers reported from respondents in Canada were:

- Wait time to treatment (was an issue or me) – 16% of respondents
- Cost of treatment – 7% of respondents

- No specialty doctor locally – 10%
- Lack of personal support – 5%
- No access to up-to-date treatment or equipment – 9%

Understanding of care and treatment

The survey also asked respondents to consider their level of understanding of their care and treatment today.

In Canada, the following % of respondents agreed/strongly agreed that they understood the following:

- surgical options 77%, n=92
- active surveillance 67%, n=77
- Adjuvant therapy (treatment aimed at reducing the chance of recurrence after surgery) 23%, n=22 (
- Ablative therapy options (cryoablation or radiofrequency ablation) 35%, n=36

5. Improved Outcomes

While new therapies in the last 15 years have led to improved patient outcomes overall, there is a general need for therapies that do more to improve the outlook for patients with advanced disease. Additionally, there is a need for effective predictive and prognostic biomarkers to guide treatment along with a need to better detect disease at earlier stages. There is also a need for more effective therapies with manageable side effects that escape resistance mechanisms to antiangiogenic therapy. Also, not all patients respond to currently available treatments, and often, patients who do respond to currently funded treatments become resistant to therapy after some time. There is a need for novel therapies that target different pathways in advanced kidney cancer.

Position Statement on Unmet Patient Needs

The following position statement on unmet patient needs has been developed based upon feedback from patient organisations representing over 1.2 million kidney cancer patients/carers across the globe. Each statement is derived from extensive patient surveys and publications of patient-generated data by the International Kidney Cancer Coalition (IKCC) and Affiliate/Partner organisations worldwide along with scientific publications outlining the limitations of existing therapies.

Unmet Needs for Patients with aRCC (All)

1. Treatments that meet patient and carer priority goals of cure/durable remission, disease stability, and long-term duration of response. [1]
2. Treatments with improved tolerability, measured with improved disease-specific quality of life (QoL) instruments and patient-report outcomes (PROs) included in all clinical trials to enable informed decision making. [2]
3. New options including new mechanisms of disease control, including novel agents beyond existing VEGF-TKI agents and checkpoint inhibitors. [3]

4. Biomarkers to reliably guide patients in their treatment selection. [4]
5. Clinical trials in heavily pretreated patients (3rd line and beyond) to provide access to agents that may offer continued disease control with acceptable tolerability/quality of life.
6. Improved shared decision making/informed decision making to ensure discussion of all multi-disciplinary treatment options including surgery, radiation, ablation, and palliative care.
7. Evidence and guidance supporting best sequencing strategies, including post-adjuvant therapy.
8. Increased access to genetic screening for hereditary syndromes per guidelines. [5]
9. Reduced barriers to quality care, including reduced financial toxicity globally. [6]
10. Increased research to meet the needs of underserved populations and populations with higher incidence of RCC. [7]
11. Improved psychosocial support for patients and their carers. [8]
12. Survivorship care plans to manage surveillance strategies, late-term effects, and quality of life. [9]

Unmet Needs for Patients with Rare Variant RCCs

1. Clinical trials for specific rare variant RCCs with goal of evidence-based treatment guidelines for specific variants. [10]
2. Access to therapies for rare variant RCCs, many of which qualify as rare cancers. [11]

References:

[1] Battle D, Vaishampayan UN, Msaouel P, et al. Patient priorities and expectations of systemic therapy in metastatic renal cell carcinoma. JCO 41(16), 4560 (2023). DOI:10.1200/JCO.2023.41.16_suppl.4560.

[2] Bergerot CD, Malhotra J, Bergerot P, et al. Patients' perceptions regarding the relevance of items contained in the functional assessment of cancer therapy kidney symptom index-19. Oncologist 28(6), 494-500 (2023). DOI:10.1093/oncolo/oyad028.

[3] Pontes O, Oliveira-Pinto S, Baltazar F, et al. Renal cell carcinoma therapy: Current and new drug candidates. Drug Discovery Today 27(1), 304-314 (2022). DOI: 10.1016/j.drudis.2021.07.009.

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[5] Lyss AP. Global survey suggests patients are underinformed, face obstacles to care. Cancer Therapy Advisor (May 5, 2023).

[6] Giles RH, Maskens D, Bick R, et al. Patient-reported experience of diagnosis, management, and burden of renal cell carcinomas: Results from a global patient survey in forty-three countries. JCO 37(15) e16091 (2019). DOI:10.1200/JCO.2019.37.15_suppl.e16091.

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[9] Giles R, Maskens D, Bick R, et al. Patient-reported experience of diagnosis, management, and burden of renal cell carcinomas: Results from a global patient survey in 43 countries. Eur Urol Open Science 37, 3-6 (2022). DOI:10.1016/j.euros.2021.12.003.

[10] Moretto P, Jewett MAS, Basiuk J et al. Kidney cancer survivorship survey of urologists and survivors: The gap in perceptions of care, but agreement on needs, Can Urol Assoc J 8(5-6), 190-194 (2014). DOI:10.5489/cuaj.1907.

[11] Giles RH, Choueiri TK, Heng DY, et al. Recommendations for the management of rare kidney cancers, Eur Urol 72(6), 974-983 (2017) DOI: 10.1016/j.eururo.2017.06.040.

[12] Naik P, Dudipala H, Chen Y-W, et al. The incidence, pathogenesis, and management of non-clear cell renal cell carcinoma. Ther Adv Urol.16 (Feb 29, 2024). DOI: 10.1177/17562872241232578.

6. Experience With Drug Under Review

Patient Interviews

DB (Interviewed on December 3, 2024)

DB is a retired 68 year old male from British Columbia. DB responded to a patient survey regarding experience with kidney cancer and the treatment "belzutifan" in early December 2024. DB also participated in a live interview in December 2024.

In 2009 at the age of 53, DB was in Montana on business and felt immense pain in his abdomen. He went to a local hospital's emergency department, where they did various scans, and identified a growth on his right kidney. When back in Canada, he was referred to a urologist in Calgary who surgically removed his right kidney.

Seven years later, and now living in Kelowna BC, he noticed a bump on his jaw line. He found a family physician who ordered various tests/biopsies. They discovered that the kidney cancer had returned. He was then referred to a medical oncologist in Kelowna who had DB enrolled in the JAVELIN Study (avelumab with axitinib versus sunitinib In advanced RCC). He received Avelumab via IV administered every two weeks, and he received Axitinib (an oral treatment) twice per day. He was on this treatment regimen for 1.5 years, but the tumour in his jaw started growing again.

DB then went to a plastic surgeon who removed the tumor. He had some scans following this procedure and a couple of months later his oncologist identified another tumor in the pleura. DB reports that his physician told him this was a very difficult location for a tumor as that location is difficult for surgery, and difficult to radiate. So, his oncologist then put him on sunitinib (Sutent). He was on this treatment for 6 months, but the tumor continued to grow. He was then prescribed pazopanib (Votrient), but early on while on pazopanib, he started to get fluid buildup in his chest cavity and had to have a chest tube inserted to drain off the fluid. He was taken off pazopanib.

With his cancer still progressing, DB was notified of a clinical trial in Vancouver, the LITESPARK-005 study: belzutifan versus everolimus in participants (pts) with previously treated RCC. DB was referred to the investigator of the trial site in Vancouver, met the inclusion criteria for the trial, was enrolled and was randomized to the belzutifan arm of the study.

For this study, DB took 120 mg of belzutifan orally once daily. Every four weeks DB was required to go to Vancouver (from Kelowna) for scans and appointments. Within 3 months DB's medical oncologist reported to him that the treatment was working very well, and that there was substantial shrinkage of tumor, and that it was barely detectable in the scans. Participating in the trial required monthly travel to Vancouver from

Kelowna , which is about a 5 hour drive (one way) in good weather. In Fall and Winter however, highway conditions can be unpredictable and dangerous, particularly through high mountain passes. So, DB decided to live closer to care and moved to Vancouver.

DB is still on the trial, and still taking belzutifan. Has been on belzutifan for 4years

When we asked: *Based on personal experience with belzutifan, how would you rate its effectiveness in controlling Kidney Cancer? 1 is "not effective" and 5 is "extremely effective",* DB rates belzutifan as "5 - **Extremely effective**"

We also asked DB, using a scale of 1-5 with 1 being "low/seriously impacted", and 5 is "high/normal living to rate his quality of life while taking belzutifan?. DB rates his quality of life, while on belzutifan, as being "4".

When we asked DB about side effect related to treatment, he replied, *"Its gets muddy. All the side effects started earlier, before starting belzutifan. The most obvious side effect I experience is neuropathy, but this started with previous treatments, but now it is way worse. I have a rash on my shins, but that started prior to the LITESPARK trial. Now, I notice some incremental tightening in my chests, some shallow breathing, and elevated blood pressure. I am taking blood pressure pills, an antacid, and something for neuropathy. And I have corticosteroid cream for the rash".*

DB reports that all the side effects are manageable, and he can still do routine activities such as going grocery shopping and riding his bike.

He reports that his tumor remains barely detectable, and that his disease is "stable". DB wants to move back to Calgary when the trial ends, but he has concerns about how moving provinces might affect his ability to continue to receive belzutifan.

RM (Interviewed on December 5, 2024)

RM is a 47-year-old married male, living in the Greater Toronto Area.

RM was originally diagnosed in 2006 with von Hippel-Lindau (VHL) Disease with tumors in his brain and on a kidney. VHL is a rare hereditary syndrome that is caused by harmful changes (also called mutations or pathogenic variants) in the VHL gene. People with VHL have an increased risk of kidney cancer and renal cysts. VHL is associated with a clear-cell type kidney cancer. Because VHL is hereditary, RM and his wife have decided to not have children.

In 2007 RM had surgery on a Kidney (partial nephrectomy) and on his brain. In 2007, after surgery, his kidney tumor returned. His medical oncologist prescribed sunitinib (Sutent) as his first line of therapy, but due side effects related to cardiomyopathy, RM was switched to axitinib (Inlyta). But later scans showed that his kidney tumor returned. RM, in 2019, was then put on nivolumab (Opdivo), an immune checkpoint inhibitor. But again, later scans showed that the tumor on his brain was again growing.

In February 2022 RM started the clinical trial for belzutifan. In Has been on belzutifan for 2 years and 10 months.

RM reports that belzutifan has been "incredibly effective" and now everything is stable, and the tumors in the brain and kidney are no longer detectable.

When we asked RM: *Based on personal experience with belzutifan, how would you rate its effectiveness in controlling Kidney Cancer? 1 is "not effective" and 5 is "extremely effective"*, RM rates belzutifan as **"5 - Extremely effective"**

We asked RM: *What specific side effects have you experienced with belzutifan? Please rate them on a scale of 1 - 5. 1 is "completely intolerable" and 5 is "very tolerable*". RM reports that he had some Fatigue/low energy, but rated that as a 4 (tolerable). He also reports some anemia and dizziness, but also rates these side effects as a "4" (tolerable). RM also reports having "low oxygen" at night while on treatment. He reports that his physicians are not sure that low oxygen is a result of therapy. RM has s pre existing (minor) sleep apnea which his doctors hypothesize may be a contributing factor. (People with obstructive sleep apnea typically have low oxygen levels due to pauses in breathing during sleep). RM says his oxygen levels are fine in the afternoons (over 95%). He is now on a CPAP machine, and he reports that oxygen levels overnight are now "fine". RM also reports that his hemoglobin count has sometimes been low while on treatment with "ups and downs".

After a lengthy journey of dealing with VHL and Kidney Cancer, including surgeries and multiple failed treatments, RM is extremely satisfied with belzutifan.

RM is still working full-time in banking.

Patient 3 (Survey response, No Interview)

One caregiver to a patient in Ontario currently using belzutifan responded to our survey, but did not consent to a live interview.

The patient (for whom this individual is a caregiver) has been on belzutifan for over 2 years through participation in a clinical trial.

We asked: Based on the patient's experience with belzutifan, how would you rate its effectiveness in controlling Kidney Cancer? 1 is "not effective" and 5 is "extremely effective". The caregiver responded: ***"5 - Extremely effective"***

We also asked: Based on your personal experience with belzutifan, overall how would you rate its side effects? 1 is "completely intolerable" and 5 is "very tolerable". The caregiver responded: ***"5 - Very tolerable"***

We also asked: If the patient did experience side effects that were particularly difficult to tolerate, please describe the side effects. The caregiver responded that the patient (while on treatment) has *"low energy level"*

We asked: What specific side effects were experienced with belzutifan? Please rate them on a scale of 1 - 5. 1 is "completely intolerable" and 5 is "very tolerable".

i) Fatigue/lack of energy *"3"*

ii) Nausea *"5 - Very tolerable"*

iii)	Anemia (low hemoglobin)	*"3"*
iv)	Dizziness	"N/A"
v)	Headache	"N/A"
vi)	Dyspnea (shortness of breath)	"N/A"
vii)	Myalgia (muscle aches and pain)	"N/A"
viii)	increased alanine aminotransferase (liver damage)	"N/A"

We asked: *On a scale of 1-5 how would you rate your quality of life while taking belzutifan? 1 is "low/seriously impacted", and 5 is "high/normal living".* The caregiver responded: *"5 - High/normal living".*

Conclusion: Not all patients respond to currently available treatments, and often, patients who do respond to currently funded treatments become resistant to therapy after some time. There is a need for novel therapies that target different pathways in advanced kidney cancer.

It is evident from KCC's engagement that some patients respond exceedingly well to belzutifan, and that belzutifan is a highly valuable treatment option in this setting.

7. Companion Diagnostic Test

Biomarkers to reliably guide patients in their treatment selection remain an unmet need.

8. Anything Else?

<Enter Response Here>

Appendix: Patient Group Conflict of Interest Declaration

To maintain the objectivity and credibility of the CADTH reimbursement review process, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This Patient Group Conflict of Interest Declaration is required for participation. Declarations made do not negate or preclude the use of the patient group input. CADTH may contact your group with further questions, as needed.

1. Did you receive help from outside your patient group to complete this submission? If yes, please detail the help and who provided it.

   No

2. Did you receive help from outside your patient group to collect or analyze data used in this submission? If yes, please detail the help and who provided it.

No

3. List any companies or organizations that have provided your group with financial payment over the past 2 years AND who may have direct or indirect interest in the drug under review.

Table 1: Financial Disclosures

Check Appropriate Dollar Range With an X. Add additional rows if necessary.

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
BMS				**X**
EISAI				**X**
IPSEN				**X**
MERCK				**X**
PFIZER				**X**

I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this patient group with a company, organization, or entity that may place this patient group in a real, potential, or perceived conflict of interest situation.

Name: Christine Collins

Position: Executive Director

Patient Group: Kidney Cancer Canada

Date: December 10, 2024

CADTH

CADTH Reimbursement Review

Clinician Group Input

CADTH Project Number: PC0386-000
Generic Drug Name (Brand Name): belzutifan (Welireg)
Indication: advanced renal cell carcinoma (RCC)
Name of Clinician Group: Kidney Cancer Research Network of Canada
Author of Submission: Dr. Vikaash Kumar

with

Dr. Tony Finelli, Chair, Kidney Cancer Research Network of Canada, Divisional Head of Urology, UHN.
Dr. Simon Tanguay, Urologic Oncologist, McGill University Health Centre, Chair, Kidney Cancer Canada Medical Advisory Board (KCC MAB).
Dr. Christian Kollmannsberger, Medical Oncologist, BC Cancer.
Dr. Maryam Soleimani, Medical Oncologist Odette Cancer Centre
Dr. Zineb Hamilou, Hématologue et Oncologue médical, Centre Hospitalier de l'Université de Montréal
Dr. Georg Bjarnason, Medical Oncologist, Odette Cancer Centre
Dr. Naveen Basappa, Medical Oncologist, Cross Cancer Institute
Dr. Rahul Bansal, Urologic Surgeon, St. Joseph's Healthcare
Dr. Dominick Bosse, Medical oncologist, University of Ottawa

1. About Your Clinician Group

The Kidney Cancer Research Network of Canada (KCRNC) is a virtual and inclusive national network of clinicians/researchers who treat kidney cancer in Canada. We are committed to the facilitation of kidney cancer care and research to enhance the knowledge of kidney cancer and its treatment. KCRNC is a federally registered not-for-profit organization.

https://www.kcrnc.ca/

2. Information Gathering

Information used to inform this submission are based on clinical experience in treating patients with metastatic renal cell carcinoma (mRCC), intimate familiarity with the published data on relevant clinical trials, and from longstanding participation in RCC research. Some of the physicians participating in this input submission were investigators in the LiteSpark-005 trial: A phase3 multicenter, open-label, active-controlled trial of Belzutifan versus Everolimus for Advanced Renal-Cell Carcinoma (ClinicalTrials.gov Identifier: NCT04195750).

3. Current Treatments and Treatment Goals

- **Below lists shows currently available and commonly used therapies in most Canadian provinces.** All listed drugs do target symptoms in patients such that patients that respond to therapy may feel better and have less pain from painful metastatic lesion. The tyrosine kinase inhibitors (TKIs) are antiangiogenic and as such modify the biology of renal cell carcinoma (RCC). The immune checkpoint inhibitors (ICIs) target the immune system thus allowing it to target the cancer cells more effectively.
- **For all IMDC risk groups:** First line (1L) options include, Pembrolizumab/Axitinib; Pembrolizumab/Lenvatinib; and, Nivolumab/Cabozantinib. Second line (2L) Cabozantinib
- **For all IMDC risk groups other options:**1L Sunitinib or Pazopanib. 2L Nivolumab, Cabozantinib or Axitinib. Third line (3L) Cabozantinib, Nivolumab or Axitinib
- **For IMDC intermediate and poor risk groups:** 1L Nivolumab/Ipilimumab. 2L Sunitinib or Pazopanib. 3L Cabozantinib or Axitinib.
- The most important goals that an ideal treatment would address include: prolonging life, reducing disease burden, and improving quality of life.

4. Treatment Gaps (unmet needs)

4.1. Considering the treatment goals in Section 3, please describe goals (needs) that are not being met by currently available treatments.

Not all patients respond to currently available treatments, and those who do often become resistant to therapy after some time. There is a need for novel therapies that target different pathways in advanced kidney cancer. Additionally, in the later lines of therapy, there is a need for treatments that offer better disease control with better side effect profiles. Having access to a different treatment option with a differing side effect profile, allows more treatment individualization and an alternative for patients who develop toxicities to TKIs. In addition, there is a need for more therapies since there are limited treatment options, and there is an increasing number of patients lacking treatment options after progressing on existing lines of therapy. Furthermore, there is a lack of

randomized phase II or III data to guide third and later line treatment of advanced RCC, and the LITESPARK-005 clinical trial has provided a much-needed clinical option in this setting.

5. Place in Therapy

5.1. How would the drug under review fit into the current treatment paradigm?

Belzutifan's mechanism of action differs from ICIs and TKIs. It is a HIF2-alpha inhibitor, preventing heterodimerization with HIF-1beta—blocking the downstream activation of proliferative pathways that contribute to angiogenesis, metastasis, and cell survival. It is being studied as well in combination with ICIs and TKIs in the metastatic setting, and in the adjuvant setting. In the LiteSpark-005 trial, Belzutifan was given in the later line setting (2L/3L/4L), after progression on ICIs and TKIs (where they may have been given as monotherapy, or in combination). Given the adjuvant and earlier line setting metastatic trials have not all completed accrual or reported findings, it would be recommended that this agent be used in the later line setting as monotherapy. Belzutifan's approval in this setting would allow an agent that offers improved progression free survival (PFS) and increased objective response to standard options in the later line setting.

5.2. Which patients would be best suited for treatment with the drug under review? Which patients would be least suitable for treatment with the drug under review?

Patients with advanced RCC who have progressed on ≥1 ICI and ≥1 TKI therapies would be best suited for Belzutifan. Patients who have progressed on ICI and TKI therapy are most in need of another option of treatment. There are instances as well, were there are contraindications to ICI therapy – renal transplant or severe autoimmune disease – where this agent could be considered. This would not differ based on disease characteristics.

5.3 What outcomes are used to determine whether a patient is responding to treatment in clinical practice? How often should treatment response be assessed?

Radiological response and symptom improvement are used to determine treatment response in clinical practice. Typically, treatment response is assessed every 3 to 4 months with imaging. The outcomes assessed in clinical practice –response to treatment, overall survival, quality of life (QOL) –are similar to the outcomes used in clinical trials. Clinically meaningful response to treatment would include complete response, partial response, or stable disease.

5.4 What factors should be considered when deciding to discontinue treatment with the drug under review?

Disease progression or unacceptable toxicity should be considered when deciding to discontinue Belzutifan. Special consideration should be given to anemia and hypoxia, both of which are well-characterized side effects of Belzutifan. Patients who experience grade II or III hypoxia may need to

hold Belzutifan and resume it at reduced dose based on the discretion of their oncologist. Patients with grade IV hypoxia must discontinue Belzutifan permanently. Patients with grade III anemia may need to hold Belzutifan and resume it at a reduced dose. Patients with grade IV anemia should discontinue Belzutifan permanently.

5.5 What settings are appropriate for treatment with [drug under review]? Is a specialist required to diagnose, treat, and monitor patients who might receive [drug under review]?

An outpatient clinic setting under the care of a Medical Oncologist with specialization in the treatment of kidney cancer is appropriate for treatment with Belzutifan.

6. Additional Information

Litespark-005 is the first phase3 study post ICI and TKI therapy that has shown a progression free survival, an overall response rate, and duration of response benefit. In this study, Belzutifan demonstrated an improved QOL when compared to Everolimus. Belzutifan offers a new mechanism of action for targeting kidney cancer. Having access to this drug, that has already obtained Food and Drug Administration approval in the United States in December 2023, would allow our Canadian patients a new and novel treatment option.

7. Conflict of Interest Declarations

To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This conflict of interest declaration is required for participation. Declarations made do not negate or preclude the use of the clinician group input. CADTH may contact your group with further questions, as needed. Please see the *Procedures for CADTH Drug Reimbursement Reviews* (section 6.3) for further details.

1. Did you receive help from outside your clinician group to complete this submission? If yes, please detail the help and who provided it.

   No.

2. Did you receive help from outside your clinician group to collect or analyze any information used in this submission? If yes, please detail the help and who provided it.

   No.

3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review. **Please note that this is required for <u>each clinician</u> who contributed to the input — please add more tables as needed (copy and paste). It is preferred for all declarations to be included in a single document.**

Declaration for Clinician

Name: Naveen Basappa
Position: Medical Oncologist
Date: 03-12-2024

☐ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 2: Conflict of Interest Declaration for Clinician

Company	Check appropriate dollar range*			
	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
Janssen	X			
EMD Serono	X			
Bayer	X			
Ipsen		X		
BMS	X			
Eisai	X			
Pfizer	X			
AstraZeneca	X			
Merck	X			
Seagen	X			
Takeda	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician

Name: Dr. Georg A Bjarnason.
Position: Professor, Faculty of Medicine, University of Toronto,
Senior Scientist, Biological Sciences Platform, Sunnybrook Research Institute,
The Anna-Liisa Farquharson Chair in Renal Cell Cancer Research
Medical Oncologist, Division of Medical Oncology, Odette Cancer Centre
Department of Medicine, Sunnybrook Health Sciences Centre
2075 Bayview Ave, Toronto, ONT, Canada, M4N 3M5

Date: 27-11 2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 2: Conflict of Interest Declaration for Clinician 2

Company	Check appropriate dollar range*			
	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
Eisai		x		
Ipsen			x	
Merck		x		
BMS		x		

* Place an X in the appropriate dollar range cells for each company.

Declaration

Name: Maryam Soleimani
Position: Medical Oncologist
Date: 02-12-2024

☐ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 2: Conflict of Interest Declaration for Clinician

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
AbbVie	X			
Astellas	X			
Bayer	X			
Ipsen		X		
Novartis	X			
Eisai	X			
Pfizer		X		
AstraZeneca	X			
Alpha-9 Oncology	X			

* Place an X in the appropriate dollar range cells for each company.

Name: **Zineb Hamilou**
Position: Medical oncologist - CHUM
Date: 2 december 2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 2: Conflict of Interest Declaration for Clinician 2

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Astra zeneca			x	
pfizer	x			
novartis	x			

Name: Vikaash Kumar
Position: Medical Oncologist, Princess Margaret Cancer Center
Date: 24-11-2024

☒ **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 1: Conflict of Interest Declaration for Clinician 1

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
IPSEN	x			
EISAI	x			
Add or remove rows as required				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician

Name: Dominick Bosse
Position: Medical oncologist, at the University of Ottawa
Date: 02 dec 2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 2: Conflict of Interest Declaration for Clinician 2

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Merck	x			
Ipsen			X (incl. research grant)	
Eisai	X			
Pfizer	x			
BMS	X			

* Place an X in the appropriate dollar range cells for each company.

Name: Rahul Bansal
Position: Associate Professor / Urologist
Date: 03-12-2024

☐ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 2: Conflict of Interest Declaration for Clinician 2

Company	Check appropriate dollar range*			
	$0 to $5,000	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Merck	x			
Knight Pharmaceuticals	x			
Mckesson	x			

Name: Simon Tanguay
Position: Urologic Oncologist / Professor
Date: 2/12/2024

☐ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 2: Conflict of Interest Declaration for Clinician 2

Company		Check appropriate dollar range*			
		$0 to $5,000	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Merck	Ad hoc advisory boards / Presentations	X			
TerSera	Ad hoc advisory boards / Presentations	X			

Declaration for Clinician

Name: <Dr. Antonio Finelli>
Position: *KCRNC Chairperson, Divisional Head of Urology (University Health Network), Professor (University of Toronto)*
Date: 06-12-2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 2: Conflict of Interest Declaration for Clinician 2

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
IPSEN				x
PFIZER			x	
MERCK				x
BMS				x
EISAI				x
INTUITIVE				x

Declaration for Clinician

Name: Christian Kollmannsberger
Position: Medical Oncologist / Clinical Professor
Date: 2/12/2024

☐ X I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 2: Conflict of Interest Declaration for Clinician 2

Company		Check appropriate dollar range*			
		$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
Pfizer	Ad hoc advisory boards / Presentations	X			
Ipsen	Ad hoc advisory boards / Presentations		X		
BMS	Ad hoc advisory boards / Presentations	X			
Astellas	Ad hoc advisory boards / Presentations	X			
Bayer	Ad hoc advisory boards / Presentations	X			
Eisai	Ad hoc advisory boards / Presentations	X			
Merck	Ad hoc advisory boards / Presentations		X		
BionTech	Ad hoc advisory board	X			
Janssen	Ad hoc advisory board	X			
Novartis	Ad hoc advisory boards / Presentations	X			

* Place an X in the appropriate dollar range cells for each company.

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CADTH

CADTH Reimbursement Review

Clinician Group Input

CADTH Project Number: PC0386
Generic Drug Name (Brand Name): belzutifan
Indication: For the treatment of adult patients with advanced renal cell carcinoma (RCC) following immune checkpoint and anti-angiogenic therapies.
Name of Clinician Group: Ontario Health (Cancer Care Ontario) Genitourinary Cancers Drug Advisory Committee ("GU DAC")
Author of Submission: Dr. Girish Kulkarni and Dr. Urban Emmenegger

1. About Your Clinician Group

OH(CCO)'s Drug Advisory Committees provide timely evidence-based clinical and health system guidance on drug-related issues in support of CCO's mandate, including the Provincial Drug Reimbursement Programs (PDRP) and the Systemic Treatment Program.

2. Information Gathering

Information was gathered via e-mail.

3. Current Treatments and Treatment Goals

First-line systemic treatment for advanced kidney cancer (i.e. aRCC) considers the IMDC risk categorization / groups. The following reflect available options in the Canadian context:

- All IMDC risk groups: Combination regimens such as pembrolizumab + axitinib; pembrolizumab + lenvatinib; or nivolumab + cabozantinib. Alternatives include sunitinib, pazopanib.
- Intermediate / poor risk groups: nivolumab + ipilimumab; alternatives sunitinib, pazopanib.

Subsequent line options include therapies not already used in the aRCC setting, such as: sunitinib, pazopanib, cabozantinib, axitinib, nivolumab

All listed drugs do target symptoms in patients such that patients that respond to therapy may feel better and have less pain from painful metastatic lesion. The tyrosine kinase inhibitors (TKIs) are mainly antiangiogenic and modify the biology of RCC. The PD-L1 checkpoint inhibitors leverage the immune system allowing it to target the cancer cells more effectively.

RCC is known to be driven by angiogenesis and thought to thrive by immune escape to some degree. Thus, therapies that inhibit angiogenesis, and activate the immune system would be of benefit.

Treatment goals include an improvement in overall survival (OS) and progression free survival (PFS) with a reduction in the size (objective response rate/ORR) of metastatic lesions in patients with aRCC, with an improved quality of life by controlling symptoms of disease

4. Treatment Gaps (unmet needs)

4.1. Considering the treatment goals in Section 3, please describe goals (needs) that are not being met by currently available treatments.

Eventually, RCC acquire resistance to the currently available treatment modalities, i.e. there is a need for novel agents with distinct mechanisms of action that are not largely cross-resistant with available agents. Oral agents are considered more patient-friendly and less resource-intense.

Belzutifan provides a different mechanism of action downstream, which is an unmet need given the lack of treatment options after failure of first line combination regimens.

5. Place in Therapy

5.1. How would the drug under review fit into the current treatment paradigm?

Belzutifan is a drug with a novel and distinct mechanism of action that targets the addiction of RCC to hypoxia signaling. Based on the available clinical data, belzutifan is considered as a second or subsequent line therapy, adding an additional line of therapy for eligible patients.

Belzutifan will be used either as second line line if the patient's disease progresses after a first line combination regimen, or as a third line line agent.

5.2. Which patients would be best suited for treatment with the drug under review? Which patients would be least suitable for treatment with the drug under review?

Belzutifan is suited for RCC patients after treatment with both a PD-1 or PD-L1 inhibitor and a VEGFR-TKI (received in sequence or in combination). Aside from the documentation of disease progression, no companion diagnostic test is needed or indicated.

Although the trial did not allow for prior everolimus, legacy patients who may have received prior everolimus should still be considered for belzutifan.

5.3 What outcomes are used to determine whether a patient is responding to treatment in clinical practice? How often should treatment response be assessed?

Standard of care to assess patient benefit to therapy include history, physical examination, and radiographic imaging (ie most commonly CT scans). This is identical to what is done with other currently funded treatment options.

Standard of care for meaningful response/benefit to patient include improved or stable clinical status (ie feeling or functioning better) and stable disease or shrinkage of disease on radiographic imaging (ie CT scan).

Clinical assessment per patient/oncologist discretion (ie in person or virtual) and imaging usually every 3 months.

5.4 What factors should be considered when deciding to discontinue treatment with the drug under review?

Unacceptable toxicity or disease progression.

5.5 What settings are appropriate for treatment with [drug under review]? Is a specialist required to diagnose, treat, and monitor patients who might receive [drug under review]?

Outpatient setting under the advisement of a medical oncologist.

6. Additional Information

7. Conflict of Interest Declarations

To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This conflict of interest declaration is required for participation. Declarations made do not negate or preclude the use of the clinician group input. CADTH may contact your group with further questions, as needed. Please see the *Procedures for CADTH Drug Reimbursement Reviews* (section 6.3) for further details.

1. Did you receive help from outside your clinician group to complete this submission? If yes, please detail the help and who provided it.

   OH (CCO) provided a secretariat function to the group.

2. Did you receive help from outside your clinician group to collect or analyze any information used in this submission? If yes, please detail the help and who provided it.

   No

3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review. **Please note that this is required for each clinician who contributed to the input — please add more tables as needed (copy and paste). It is preferred for all declarations to be included in a single document.**

Declaration for Clinician 1

Name: Dr. Girish Kulkarni
Position: Lead, OH-CCO GU DAC
Date: 21-Nov-2024

☒ **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

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	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 2

Name: Dr. Urban Emmenegger
Position: Member, OH-CCO GU DAC
Date: 12-November-2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 2: Conflict of Interest Declaration for Clinician 2

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Merck		x		

* Place an X in the appropriate dollar range cells for each company.