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CADTH Reimbursement Recommendation

Lenvatinib (Lenvima) in Combination With Pembrolizumab (Keytruda)

Indication: Treatment of adult patients with advanced (not amenable to curative surgery or radiation) or metastatic renal cell carcinoma (RCC) with no prior systemic therapy for metastatic RCC

Sponsor: Eisai Limited

Final recommendation: Reimburse with conditions

CADTH

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

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Summary

CADTH

What Is the CADTH Reimbursement Recommendation for Lenvima in Combination With Keytruda?

CADTH recommends that Lenvima in combination with Keytruda be reimbursed by public drug plans for the treatment of adult patients with advanced or metastatic renal cell carcinoma (RCC) who have had no prior systemic therapy for metastatic disease if certain conditions are met.

Which Patients Are Eligible for Coverage?

Lenvima in combination with Keytruda should only be covered in patients aged 18 years and older with advanced (that cannot be cured with surgery or radiation) or metastatic (that has spread to other organs) RCC who have not received prior systemic therapy for advanced RCC.

What Are the Conditions for Reimbursement?

Lenvima in combination with Keytruda should be reimbursed if prescribed under supervision in an outpatient oncology clinic or institution with expertise in delivering systemic therapy. Lenvima in combination with Keytruda should only be reimbursed when administered in combination and if cost is reduced.

Why Did CADTH Make This Recommendation?

Evidence from a clinical trial demonstrated that people with advanced or metastatic RCC treated with Lenvima in combination with Keytruda experienced a delay in the spread of cancer and lived longer.

Based on CADTH's assessment of the health economic evidence, Lenvima in combination with Keytruda does not represent good value to the health care system at the publicly listed price. Over a 3-year period, Lenvima in combination with Keytruda is expected to increase drug costs to the public plans by more than $40 million. Therefore, for Lenvima in combination with Keytruda to be cost-effective compared with axitinib plus pembrolizumab at a willingness-to-pay threshold of $50,000 per quality-adjusted life-year, a 56% reduction in the price of Lenvima is required.

Additional Information

What Is RCC?

RCC is a cancer that begins from the lining of the kidney tubules, the main function of which is to filter and clean blood to remove waste materials. People with advanced or metastatic RCC have cancer that has spread to other organs or body parts, such as the bones, adrenal glands, brain, and the liver.

Unmet Needs in RCC

Patients with advanced RCC are in need of alternative treatment options with a different or better toxicity profile and improved health benefits.

How Much Does Lenvatinib Cost?

The total cost for a 21-day treatment cycle with Lenvima in combination with Keytruda is estimated to be $12,484 or $216,978 annually, if patients were to remain on the treatment for a full year.

Recommendation

The CADTH pCODR Expert Review Committee (pERC) recommends that lenvatinib (LEN) combined with pembrolizumab (PEM) be reimbursed for the treatment of adult patients with advanced (not amenable to curative surgery or radiation) or metastatic renal cell carcinoma (RCC) who have had no prior systemic therapy for metastatic disease only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

One multi-centre, randomized, parallel-arm, open-label, phase III trial (CLEAR, N = 712) demonstrated that treatment with LEN-PEM resulted in added clinical benefit compared with sunitinib (SUN) in patients with advanced or metastatic RCC in all International mRCC Database Consortium (IMDC) risk groups who have not received prior treatment in the first-line setting. The CLEAR trial showed a statistically significant and clinically meaningful improvement in progression-free survival (PFS) with LEN-PEM compared with SUN (hazard ratio [HR] = 0.39; 95% CI, 0.32 to 0.49; P < 0.0001). Treatment with LEN-PEM also showed a statistically significant and clinically meaningful improvement in overall survival (OS) with an HR of 0.66 (95% CI, 0.49 to 0.88; P = 0.0049), although these results are associated with some uncertainty due to data immaturity. Patients treated with LEN-PEM appeared to have better maintenance of health-related quality of life (HRQoL) and less severe symptoms compared with treatment with SUN, although pERC was unable to draw definitive conclusions due to the absence of formal statistical testing. pERC considered the safety profile of LEN-PEM to be manageable, albeit more burdensome, than SUN. Limited evidence from indirect treatment comparisons (ITCs) suggested that LEN-PEM has similar or potentially better PFS benefits compared with other combination therapies, such as axitinib (AXI) plus PEM or ipilimumab plus nivolumab.

Patients identified the following needs: reduce or control disease, improve survival in advanced disease, reduce cancer symptoms, enhance HRQoL, and avoid deleterious side effects. Given the totality of the evidence, pERC concluded that LEN-PEM met some of the needs identified by patients by delaying disease progression, potentially improving OS, and potentially maintaining or improving HRQoL. LEN-PEM also presents a different toxicity profile than other therapies in this setting, which may address an unmet need in patients who cannot tolerate alternative drugs.

Using the sponsor-submitted price for LEN and publicly listed prices for all other drug costs, treatment with LEN-PEM was associated with higher costs to the health care system than AXI-PEM and considered similarly effective. As such, LEN-PEM should cost no more than the least costly immunotherapy plus tyrosine kinase inhibitor (TKI) regimen for adult patients with advanced or metastatic RCC with no prior systemic therapy for metastatic RCC.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Treatment with LEN-PEM should only be reimbursed when initiated in adults (18 years or older) with advanced (not amenable to curative surgery or radiation) RCC who have not received prior systemic therapy for advanced RCC.	Evidence from the CLEAR trial demonstrated a clinical benefit in patients who fulfilled these characteristics.	Patients with non-clear cell histology may be treated in the same manner as those with clear cell histology due to the absence of standard treatment options for patients with non-clear cell histology.
2. Patients should have good performance status.	Patients with KPS of ≥ 70% were included in the CLEAR trial.	Treating patients with KPS < 70% may be at the discretion of the treating clinician.
3. Patients must not have any of the following: 3.1. active CNS metastases 3.2. active autoimmune disease.	The CLEAR trial excluded patients with active CNS metastases and autoimmune disease. There is no evidence to suggest these patients will benefit from treatment with LEN-PEM.	Patients with treated or stable CNS metastases should be eligible for treatment. Treatment of patients with autoimmune disease may be at the discretion of the treating physician.
Discontinuation		
4. Discontinuation should be based on a combination of clinical/ radiological progression and significant adverse events potentially related to LEN-PEM.	Consistent with clinical practice, patients from the CLEAR trial discontinued treatment upon progression or unacceptable toxicity.	—
5. PEM should be reimbursed for a maximum of 35 cycles (for 200 mg dosing), or 18 cycles (for 400 mg dosing), or 2 years, whichever is longer. LEN can be continued beyond this time.	Patients in the CLEAR trial were treated with PEM for a maximum of 35 cycles.	It would be reasonable to re-administer PEM (up to 17 additional administrations of 200 mg), with or without LEN, at the discretion of the treating physician for patients who have discontinued PEM at the time of relapse only if the treatment was discontinued before disease progression or disease progression occurred during a treatment break.
Prescribing		
6. LEN-PEM should be prescribed in an outpatient oncology clinic; treatment should be supervised and/or delivered in institutions with expertise in systemic therapy delivery.	To ensure that LEN-PEM is prescribed only for appropriate patients and adverse effects are managed in an optimized and timely manner.	PEM may be given at a dose of 400 mg IV every 6 weeks instead of 200 mg IV every 3 weeks. It can be given based on weight at 2 mg/kg up to 200 mg every 3 weeks or 4 mg/kg up to 400 mg every 6 weeks.

Reimbursement condition	Reason	Implementation guidance
7. LEN-PEM should only be reimbursed when administered in combination.	There are no data supporting the efficacy and safety of LEN-PEM when used in combination with additional anticancer drugs, or when either component is initially used as monotherapy.	As stated in Reimbursement Condition 5, LEN can continue as monotherapy after the 35 cycles of PEM.
Pricing		
8. LEN-PEM should be negotiated so that it does not exceed the drug program cost of treatment with the least costly immunotherapy plus TKI regimen reimbursed for the treatment of adult patients with advanced or metastatic RCC with no prior systemic therapy for metastatic RCC regardless of IMDC risk status.	There is insufficient evidence to justify a cost premium for LEN-PEM over the least expensive immunotherapy plus TKI regimen reimbursed for advanced or metastatic RCC with no prior systemic therapy for metastatic RCC regardless of IMDC risk status. Limited evidence from indirect treatment comparisons suggested that LEN-PEM results in similar or potentially better PFS benefits compared with AXI-PEM. The NMA was not suggestive of an OS benefit for LEN-PEM compared with AXI-PEM.	—
Feasibility of adoption		
9. The feasibility of adoption of LEN-PEM must be addressed.	At the submitted price, the budget impact of LEN-PEM is expected to be greater than $40 million in year 3.	—

AXI = axitinib; CNS = central nervous system; IMDC = International Metastatic RCC Database Consortium; KPS = Karnofsky Performance Status; LEN = lenvatinib; NMA = network meta-analysis; OS = overall survival; PEM = pembrolizumab; PFS = progression-free survival; RCC = renal cell carcinoma; TKI = tyrosine kinase inhibitor.

Discussion Points

- pERC noted that patients with advanced RCC are in need of alternative treatment options with a different or better toxicity profile and improved outcomes across all IMDC risk groups.
- pERC discussed the generalization of the trial results to all RCC histologies (clear cell and non-clear cell variants). pERC noted that patients with non-clear cell tumours were excluded from the CLEAR study. However, pERC expected all histologies to respond to LEN-PEM, as they do with other therapies in this setting. Therefore, tumour histology should not be a limiting factor for reimbursement of this regimen, and all advanced RCC histologies should be covered.
- pERC agreed with the clinical experts that, in comparison with AXI-PEM (the most relevant comparator), LEN-PEM may offer a different toxicity profile that would help address clinical issues in some patients, particularly in terms of liver toxicity. However, there was no direct evidence comparing the safety of these 2 regimens.
- pERC discussed results of ITCs reviewed by CADTH. Interpretation of the sponsor-submitted network meta-analysis (NMA) was limited due to methodological issues, such as connections being limited to 1 study, concerns with potential bias due to effect modifiers, trial population heterogeneity, and lack of reporting of study quality

assessments and study withdrawals. However, results were suggestive of better PFS comparing LEN-PEM to pazopanib and nivolumab plus ipilimumab, and similar PFS when compared with AXI-PEM, although OS data were too immature to draw conclusions and HRQoL was not analyzed. pERC agreed with the clinical experts that LEN-PEM would provide a viable alternative option for patients who are candidates for immuno-oncology and TKI combination treatment.

- pERC noted that no multiplicity adjustments were made during the analysis of duration of response (DOR), disease control rate (DCR), HRQoL, and defined subgroups in the CLEAR trial. Thus, pERC considered findings related to these outcomes to be exploratory and supportive in nature.
- pERC noted substantial uncertainty in the economic analysis, including the lack of direct comparative PFS evidence for LEN-PEM versus AXI-PEM and the immaturity of OS data. In the absence of clear demonstrated differences in safety and effectiveness between these 2 regimens, pERC suggested that LEN-PEM should not be priced higher than AXI-PEM.
- pERC noted that the drug cost of LEN-PEM is lower than the drug cost of AXI-PEM. The price reduction recommendation is made based on the estimate of the total treatment cost from the pharmacoeconomic analysis, which was higher for LEN-PEM. This cost increase was influenced by the anticipated longer progression-free interval for patients treated with LEN-PEM based on findings from the sponsor's NMA.

Background

RCC is the most common form of kidney cancer, accounting for more than 85% of all cases around the world. RCCs are further classified into different subtypes based on histology (clear cell, papillary, chromophobe, clear cell papillary, collecting duct, medullary, and unclassified). The clear cell component is the most prevalent form of RCC and represents more than 70% of all RCC cases in practice. More than 33% of cases identified at initial diagnosis have metastatic disease due to the fact that most patients experience few or no symptoms at earlier stages, which restricts the number of cases identified with early disease. Common symptoms are blood in the urine, constant dull pain around the flank region, fullness or a lump in the upper abdomen, fever, appetite loss, nausea, vomiting, constipation, weakness, fatigue, anemia, polycythemia, or unexplained weight loss. Projected estimates in Canada in 2021 show that kidney and renal pelvis cancers were the seventh most diagnosed cancers in men (5,200 new cases; 2.8% disease-related deaths) and the 12th most diagnosed cancers in women (2,600 new cases; 1.7% disease-related deaths). The predicted 5-year age-standardized survival was 73% for both sexes. Established risk factors include smoking, hypertension, obesity, medications (over-the-counter pain killers, phenacetin-containing compounds, and diuretics), family history of RCC, and genetic conditions (von Hippel-Lindau disease) or hereditary papillary RCC.

Treatment selection in practice is based on prognostic risk models, particularly the IMDC risk group classifications (favourable, intermediate, and poor). For patients within the "favourable" risk group category, preferred therapies outlined by the Kidney Cancer Research Network of Canada (KCRNC) practice guideline include AXI-PEM or nivolumab plus cabozantinib (which is not a reimbursed regimen). Other options include SUN and pazopanib. For patients within the "intermediate/poor" risk group category, the preferred options include ipilimumab plus nivolumab, AXI-PEM, and nivolumab plus cabozantinib. Other available options for this risk

group include SUN, pazopanib, and cabozantinib (cabozantinib recently acquired market approval from Health Canada on October 6, 2021, as a first-line treatment option for patients with advanced RCC within the intermediate/poor IMDC risk group category). However, first-line cabozantinib was not reviewed by CADTH and is not currently reimbursed.

LEN is approved by Health Canada for the following indication: in combination with PEM for the treatment of adult patients with advanced (not amenable to curative surgery or radiation) or metastatic RCC with no prior systemic therapy for metastatic RCC. LEN is a multiple-receptor TKI, and PEM is a high-affinity antibody against PD-1, which exerts dual ligand blockade of the PD-1 pathway, including PD-L1 and PD-L2, on antigen-presenting or tumour cells. LEN is available as a capsule in 4 mg and 10 mg doses. The proposed recommended dosage for patients with advanced RCC in the product monograph is 20 mg (two 10 mg capsules) orally once daily in combination with pembrolizumab, which is administered as an IV infusion over 30 minutes every 3 weeks.

Sources of Information Used by the Committee

To make their recommendation, the committee considered the following information:

- a review of 1 phase III randomized clinical trial in patients with advanced or metastatic RCC
- patient perspectives gathered by 2 patient groups: CanCertainty and Kidney Cancer Canada
- input from public drug plans and cancer agencies that participate in the CADTH review process
- 2 clinical specialists with expertise diagnosing and treating patients with advanced or metastatic RCC
- input from 2 clinician groups; The Ontario Health (Cancer Care Ontario) Genitourinary Drug Advisory Committee (OH-CCO) Drug Advisory Committee and KCRNC
- 1 sponsor-submitted ITC and 4 published ITCs
- a review of the pharmacoeconomic model and report submitted by the sponsor.

Stakeholder Perspectives

Patient Input

Two patient groups, CanCertainty and Kidney Cancer Canada, provided input for this submission.

The CanCertainty group expressed concerns related to inconsistent provincial coverage for oncology treatment regimens containing orally administered drugs and the resulting financial burden in vulnerable patients.

The Kidney Cancer Canada group included 2 online surveys of patients with kidney cancer and caregivers that were conducted in 2018 (KCC survey) and 2020 (IKCC survey: 241 Canadian respondents of whom 47% had no evidence of disease, 6% had local disease

and 35% had advanced/metastatic disease) and 1 patient telephone interview conducted on November 26, 2021. In the IKCC survey, patients reported that no access to up-to-date treatment or equipment is 1 of the top barriers to treatment. The most-reported side effects of kidney cancer therapies in the KCC survey included fatigue or lack of energy, diarrhea, loss of appetite, hand-foot syndrome, skin problems including itching and rash, nausea or vomiting, pain, shortness of breath, and bleeding. Approximately one-fourth of patients indicated the treatment was difficult to tolerate. Patients highlighted that improved physical condition, such as tumour response and symptom control (breathing and pain); QoL improvement; and a chance for long-term disease control were highly important considerations before taking a new therapy. One clinical trial participant who was interviewed about his experience with LEN-PEM for metastatic RCC described the treatment as effective, very tolerable, with manageable side effects (e.g., total body rash managed with prednisone, nausea, fatigue, reduced appetite), and a reasonable QoL.

Clinician Input

Input From Clinical Experts Consulted by CADTH

The clinician experts consulted during this CADTH review considered prolonged OS and PFS, reduction in metastatic lesions (objective response rate [ORR]), and improved quality of life as the most important treatment goals. The experts noted that not all patients respond to treatments, and some patients become resistant to therapy in the long run.

The clinician experts considered ORR, PFS, and OS clinically meaningful to patients with metastatic RCC. According to the experts, a clinically meaningful response to treatment is associated with a reduction in the size of metastatic disease seen by CT imaging, reduction in pain from local metastases, and generally improved well-being of the patient. The clinician experts stated that CT imaging, history, and physical examination are commonly used to assess patient response to therapy in practice, and that assessments are conducted every 2 to 3 months. The clinician experts highlighted disease progression or serious autoimmune side effects related to PEM as deciding factors for treatment discontinuation. The clinician experts consulted thought that LEN-PEM will provide an additional treatment option for patients with metastatic RCC in the first-line setting, and patients in all IMDC risk groups will benefit from LEN-PEM.

One clinician expert highlighted that the significant benefit of treatment with LEN-PEM over AXI-PEM is the much lower liver toxicity associated with LEN, and cited that the incidence of liver toxicity with AXI-PEM is between 22% to 29%. In the opinion of the experts, differentiating the causes of liver toxicity in patients in practice following the use of AXI over immunotherapy is challenging and it is often responsible for prolonged breaks off all therapy. As highlighted by 1 expert, the toxicity may be lower with LEN-PEM in terms of hepatotoxicity; however, the full toxicity profile of the combinations will only be evident in their use outside of the clinical trial setting.

Clinician Group Input

This section was prepared by CADTH staff based on the input provided by patient groups. The full clinician group input is included in the Stakeholder section of this review.

Two clinician groups provided input for this CADTH review. The OH-CCO's Drug Advisory Committee is a group that provides 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. The KCRNC is a virtual and inclusive national network of researchers committed to the facilitation of kidney cancer research to enhance the knowledge of kidney cancer and its treatment.

Both clinician groups highlighted improved OS and PFS, reduction in tumour size (measured as ORR), and improved quality of life as treatment goals. Both clinician groups identified treatment options that were consistent with those listed by KCRNC practice guidelines for kidney cancer management. Both clinician groups identified poor response and resistance to treatment as issues faced by patients and clinicians with current treatment options. Both clinician groups anticipated that LEN-PEM will be an effective first-line option for patients with advanced RCC. Both groups considered the PFS and ORR findings from the CLEAR trial clinically significant.

Drug Program Input

Input was obtained from the drug programs that participate in the CADTH reimbursement review process. The clinical experts consulted by CADTH provided advice on the potential implementation issues raised by the drug programs.

Table 2: Summary of Drug Plan Input and Clinical Expert Response

Implementation issues	Response
Relevant comparators	
Is there a preferred first-line treatment for specific patient populations?	pERC was unable to advise on the preferred first-line treatment due to the lack of comparative evidence. Choice of therapy may be dependent on the individual patient, in discussion with the treating oncologist.
Considerations for initiation therapy	
Should patients with stable CNS metastases be eligible for LEN-PEM?	pERC indicated that patients with stable CNS metastases were included in the CLEAR trial. Patients with stable or treated brain metastases should be eligible for LEN-PEM. However, patients with new or unstable CNS metastases are not eligible to receive therapy.
In the CLEAR trial, patients who received prior systemic anticancer therapy for RCC (including adjuvant therapy) were excluded. Should patients who complete or discontinue PEM in the adjuvant setting without disease progression, and have a disease-free interval of 6 months or greater, be eligible for LEN-PEM?	pERC noted that such patients should be eligible for treatment, although there is no available evidence. pERC agreed with the clinical expert that it will be reasonable to re-initiate treatment if a patient who completed or discontinued PEM in the adjuvant setting without disease progression and had a disease-free interval of 6 months or greater. pERC noted that this adjuvant therapy is not yet standard of care in Canada.
Should patients who complete 2 years of PEM and experience disease progression/recurrence off PEM treatment be eligible for up to 1 year (17 cycles) of re-treatment?	pERC noted that the CLEAR trial did not permit re-treatment at recurrence. However, pERC considered that it would be reasonable to re-administer PEM (up to 17 additional cycles), without LEN, at the discretion of the treating physician for patients who have discontinued PEM at the time of relapse, but only if the treatment was discontinued before disease progression or disease progression occurred during a PEM treatment break. This would be consistent with pERC guidance on PEM for other indications.

Implementation issues	Response
Considerations for discontinuation of therapy	
If 1 drug in the combination treatment is discontinued for reasons other than progression (e.g., discontinued due to toxicity), should the other drug be continued?	pERC agreed with the clinical experts that, in practice, patients can continue with 1 drug if the other drug in the treatment combination is not well tolerated or discontinued.
Considerations for prescribing of therapy	
Some jurisdictions may implement weight-based dosing up to a maximum dose for PEM (i.e., 2 mg/kg up to a maximum dose of 200 mg every 3 weeks). Should PEM 4 mg/kg (up to a maximum dose of 400 mg) IV every 6 weeks be an option?	In the opinion of the clinical experts, PEM dosing of 4 mg/kg (up to a maximum dose of 400 mg) IV every 6 weeks should be made available as an option from provincial drug plans. pERC agreed that weight-based dosing up to a cap would be a reasonable alternative to flat dosing.
Generalizability	
The CLEAR trial eligibility criteria limited enrolment to patients with a clear cell component. Are the results of the CLEAR trial generalized to patients with non-clear cell metastatic RCC?	pERC indicated that although the data cannot be extrapolated to patients with non-clear cell RCC, in clinical practice these patients are treated in the same manner due to the absence of standard treatment options for non-clear cell RCC. Hence, treatment should be as per the indicated target population of "advanced or metastatic RCC."
The CLEAR trial was stratified based on MSKCC prognostic group. Is there a prognostic risk group more likely to derive benefit from LEN-PEM?	pERC and clinician experts believed that all 3 risk groups will benefit from the treatment, as is the case for AXI-PEM in clinical practice.
Should patients currently receiving alternate first-line therapy, who have not yet progressed, be eligible to switch to LEN-PEM?	pERC noted that no switching should be required if a patient is responding adequately, although it may depend on the therapy a patient is currently receiving. Switching should be allowed for toxicity reasons as long as the patient has not progressed on the previous treatment or if the patient cannot tolerate an adequate dose of a regimen. Clinician judgment should be exercised.
Funding algorithm	
Drug may change place in therapy of comparator drugs.	pERC considered that this new therapy would be an alternative first-line option and would not change the place in therapy of other drugs, although it may displace them from the market.
Drug may change place in therapy of drugs reimbursed in subsequent lines.	pERC expects subsequent lines of therapy after LEN-PEM to be funded in a similar manner as they currently are after AXI-PEM because the same principles and data apply.

Implementation issues	Response
Care provision issues	
LEN capsules are available as 4 mg and 10 mg capsules. The variety of potential daily doses are available from the manufacturer, packaged in blister cards of 5-day increments. This packaging provides flexibility for dispensing different durations of therapy, although it may require pharmacies to carry multiple different strengths of blister cards to anticipate the multiple doses that may be clinically indicated. Dose modifications for LEN in clinical practice are anticipated to be common because of the high frequency of dose modifications reported in the CLEAR trial (84.4% of patients required LEN dose modifications). In addition, if dose reductions are required between prescription fills (e.g., mid-cycle), drug wastage would occur for any previously dispensed supply of LEN because these cannot be re-dispensed.	pERC acknowledged the issues of drug packaging and wastage. pERC suggested that the pricing of the various sizes should be clarified with the manufacturer. pERC noted that patient education and counselling will be necessary to avoid over- or underdosing with LEN.

AXI = axitinib; CNS = central nervous system; LEN = lenvatinib; MSKCC = Memorial Sloan Kettering Cancer Center; PEM = pembrolizumab; pERC = CADTH pCODR Expert Review Committee; RCC = renal cell carcinoma.

Clinical Evidence

Pivotal Studies and Protocol-Selected Studies

Description of Studies

The CLEAR trial is an ongoing multi-centre, randomized, parallel-arm, open-label, phase III study. The primary objective of the CLEAR trial was to compare the efficacy and safety of LEN in combination with either everolimus or PEM versus SUN as first-line treatment in adult patients with advanced RCC. The study enrolled patients who were 18 years and older, with a histologically or cytologically confirmed diagnosis of RCC with a clear cell component and documented evidence of advanced disease. Patients were also required to have at least 1 measurable target lesion by Response Evaluation Criteria in Solid Tumours Version 1.1 (RECIST 1.1) criteria; adequate liver, bone marrow, blood coagulation, and renal function; a Karnofsky Performance Status (KPS) score of 70 or greater; and adequately controlled blood pressure with or without antihypertensive medications.

The primary outcome investigated in the CLEAR trial was PFS measured by independent imaging review (IIR) using the RECIST 1.1 criteria. Secondary and exploratory outcomes include OS, ORR, HRQoL (from 3 questionnaires: Functional Assessment of Cancer Therapy Kidney Symptom Index–Disease-Related Symptoms [FKSI-DRS], the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 [EORTC QLQ-C30], and the EQ-5D-3L with the associated EuroQoL Visual Analogue Scale [EQ-VAS]), safety and tolerability, DOR, and DCR.

Patients were randomized into 3 study arms (LEN-PEM, LEN plus everolimus, and SUN) in a 1:1:1 ratio based on 2 stratification factors: geographic region and the Memorial Sloan Kettering Cancer Center (MSKCC) prognostic risk groups. There were more than 200

participating sites across North America (with 6 sites in Canada), Europe, Asia, and Australia. Patients received either 20 mg of LEN orally, daily with 200 mg of PEM intravenously every 3 weeks or 50 mg of SUN orally, daily every 4 weeks followed by 2 weeks off treatment (schedule 4/2) until the investigator discontinued treatment for the patient, patient withdrew consent, or patient moved into the follow-up phase. This CADTH review focuses on the comparison between LEN-PEM and SUN as per the sponsor's reimbursement request and the pre–Notice of Compliance Health Canada indication.

By the third interim analysis data cut-off (August 28, 2020), a total of 1,417 patients had been screened, of which 1,069 were randomized to receive a study treatment in 1 of the 3 study arms. In total, 355 patients were randomized into the LEN-PEM arm and 357 patients were randomized into the SUN arm. The median age of patients enrolled in the CLEAR study was 62 years; more men were enrolled than women and the majority of patients were White or Asian. Baseline characteristics were equally distributed between the 2 study arms except for age (more patients randomized into the SUN arm were younger than 65 years compared with the LEN-PEM arm). More patients discontinued treatment in the SUN arm (76.5%) compared with the LEN-PEM arm (59.2%), and more patients in the SUN arm (57.7%) received subsequent systemic anticancer medication during survival follow-up compared with the LEN-PEM arm (33%).

Efficacy Results

Progression-Free Survival

By the third interim data cut-off (August 28, 2020), a total of 365 PFS events had occurred. The median PFS was 23.9 (95% CI, 20.8 to 27.7) months in the LEN-PEM arm and 9.2 (95% CI, 6.0 to 11.0) months in the SUN arm. The HR obtained between the LEN-PEM arm versus SUN arm was 0.39 (95% CI, 0.32 to 0.49, P < 0.0001). The estimated median PFS follow-up was 22.3 (95% CI, 21.1 to 25.6) months in the LEN-PEM arm and 16.6 (95% CI, 13.1 to 18.5) months in the SUN arm.

PFS in the subgroups of interest (risk groups by the IMDC prognostic model) were as follows:

- **Favourable risk group:** The estimated median PFS was 28.1 months in the LEN-PEM arm and 12.9 months in the SUN arm. The HR between the LEN-PEM arm versus the SUN arm was 0.41 (95% CI, 0.28 to 0.62).
- **Intermediate risk group:** The estimated median PFS in the LEN-PEM arm was 22.1 months and 7.1 months in the SUN arm. The HR obtained between the LEN-PEM arm and SUN arm was 0.39 (95% CI, 0.29 to 0.52).
- **Poor risk group:** The estimated median PFS in the LEN-PEM arm was 22.1 months and 4 months in the SUN arm. The HR between the LEN-PEM arm versus the SUN arm was 0.28 (95% CI, 0.13 to 0.60).

Objective Response Rate

The estimated ORR by IIR in the LEN-PEM arm at the August 28, 2020, data cut-off was 71% (95% CI, 66.3% to 75.7%). In total, 16.1% of patients receiving LEN-PEM had a confirmed complete response and 54.9% had a confirmed partial response. In the SUN arm, the estimated ORR was 36.1% (95% CI, 31.2% to 41.1%). In total, 4.2% of patients receiving SUN had a confirmed complete response and 31.9% had a confirmed partial response. The estimated odds ratio in the LEN-PEM arm versus the SUN arm was 4.35 (95% CI, 3.16 to 5.97) in favour of LEN-PEM (P < 0.0001).

Overall Survival

The median OS by IIR was not estimable in either treatment arm at the August 28, 2020, data cut-off (interim 3) or at the subsequent follow-up analysis performed on March 31, 2021. The estimated HR between the LEN-PEM arm versus the SUN arm was 0.66 (95% CI, 0.49 to 0.88; P = 0.0049).

The median duration of follow-up at the August 28, 2020, data cut-off was 26.7 (95% CI, 25.9 to 27.4) months in the LEN-PEM arm and 26.3 (95% CI, 25.4 to 27.2) months in the SUN arm. At the March 31, 2021, data cut-off, median OS was not estimable. The estimated HR between the LEN-PEM arm and SUN arm was 0.72 (95% CI, 0.55 to 0.93). The median duration of follow-up was 33.7 (95% CI, 32.8 to 34.4) months in the LEN-PEM arm and 33.4 (95% CI, 32.5 to 34.1) months in the SUN arm.

Duration of Objective Response

By the August 28, 2020, data cut-off, the median DOR observed in patients was 25.8 (95% CI, 22.1 to 27.9) months in the LEN-PEM arm and 14.6 (95% CI, 9.4 to 16.7) months in the SUN arm.

Health-Related Quality of Life

The HRQoL assessment between the LEN-PEM arm and the SUN arm for the EORTC QLQ-C30 questionnaire for physical function was an overall least squares mean difference of 3.01 (95% CI, 0.48 to 5.54) measured after 46 weeks of treatment and the following for symptom scales: fatigue (−2.8; 95% CI, −5.52 to −0.08), dyspnea (−2.79; 95% CI, −5.53 to −0.25), and constipation (−2.19; 95% CI, −4.19 to −0.18).

Time-to-First-Deterioration Assessments

EORTC QLQ-C30 questionnaire: In physical functioning, the median time to first deterioration (TTD) for the LEN-PEM arm was 15.29 (95% CI, 12.29 to 21.43) weeks; in the SUN arm, median TTD was 12.71 (95% CI,9.29 to 18.14; nominal log rank difference P = 0.03) weeks. The median TTD in weeks obtained in the dyspnea subscale was 39.29 (95% CI, 24.43 to 51) in the LEN-PEM arm and 21.14 (95% CI, 15.43 to 32.71) in the SUN arm (nominal log rank difference P value = 0.02). In the appetite loss subscale, the median TTD in the LEN-PEM arm was 18.29 (95% CI, 15.14 to 21.71); in the SUN arm, the median TTD was 9.14 (95% CI, 6.29 to 15.14). The nominal P value of the log rank test was 0.03.

EQ-5D-3L VAS: The median TTD obtained in the VAS was 9.43 (95% CI, 6.43 to 12.29) in the LEN-PEM arm and in the SUN arm, the median TTD was 9.14 (95% CI, 6.29 to 12.0). A nominal P value of 0.04 was obtained in the log rank difference test.

Time Until Definitive Deterioration

FKSI-DRS total score: In the LEN-PEM arm, the median time until definitive deterioration (TUDD) was 134.14 (95% CI, 120 to not estimable [NE]) weeks; in the SUN arm, the TUDD was 117.43 (95% CI, 90.14 to 131.29) weeks. The nominal P value obtained was less than 0.01.

EORTC QLQ-C30: The median TUDD in the Global Health Score/QoL in weeks in the LEN-PEM arm was 114.29 (95% CI, 102.14 to 153.29); in the SUN arm, the median TUDD was 75.14 (95% CI, 57.29 to 105.14). The nominal P value obtained was less than 0.0001.

In the physical function domain of the EORTC, the median TUDD in the LEN-PEM arm was 134.14 (95% CI, 109.14 to NE); in the SUN arm, the median TUDD in weeks was 78.14 (95%

CI, 63.14 to 111.0). The nominal P value obtained from the log rank difference was less than 0.0001.

EQ-5D-3L VAS: The median TUDD in weeks obtained in the LEN-PEM arm was 124.86 (95% CI, 94.71 to 134.57); in the SUN arm, the median TUDD in weeks was 74.86 (95% CI, 54.14 to 94.0). The nominal P value obtained was less than 0.01.

Disease Control Rate

By the August 28, 2020, data cut-off, the DCR observed in the LEN-PEM arm was 90.1%; in the SUN arm, the DCR was 74.2%.

Time to Treatment Discontinuation

This outcome was not investigated in the CLEAR trial.

Harms

Overall, the proportion of patients reporting at least 1 adverse event (AE) was comparable in both study arms (99.7% in the LEN-PEM arm and 98.5% in the SUN arm) by the August 28, 2020, data cut-off. Diarrhea, hypertension, hypothyroidism, decreased appetite, fatigue, nausea, and stomatitis were the most common AEs reported in the LEN-PEM arm; diarrhea, hypertension, stomatitis, PPE syndrome, fatigue, nausea, and decreased appetite were most commonly reported in the SUN arm.

Serious AEs were reported in 50.6% of patients in the LEN-PEM arm compared with 33.2% in the SUN arm. There were more AEs leading to drug discontinuations (37.2% versus 14.4%), dose reductions (68.8% versus 50.3%), drug interruptions (78.4% versus 53.8%), and dose modifications (87.5% versus 70.3%) in the LEN-PEM arm compared with the SUN arm. Overall, more deaths were reported in the SUN arm (29.1%) compared with the LEN-PEM arm (22.2%).

The following notable harms were reported in the LEN-PEM and the SUN arm: hypertension (56.3% versus 42.6%), hypothyroidism (56.8% versus 32.1%), hepatotoxicity (27.3% versus 24.1%), proteinuria (29.5% versus 12.6%), hemorrhage (27.3% versus 26.5%), palmar-plantar erythrodysesthesia syndrome (29.5% versus 37.9%), renal events (22.2% versus 17.6%), QT prolongation (6.5% versus 3.8%), arterial thromboembolic events (5.4% versus 2.1%), gastrointestinal perforation (1.4% versus 0.9%), hypocalcemia (1.4% versus 2.6%), cardiac dysfunction (2.6% versus 2.1%), fistula formation (0.6% versus 0.6%), and posterior reversible encephalopathy syndrome (0.6% versus 0.3%) were the notable harms observed in the LEN-PEM and SUN arms, respectively.

Critical Appraisal

The CLEAR trial is a randomized, parallel-arm study. The randomization scheme minimized the risk of bias caused by unknown confounders, including known and unknown prognostic factors. Baseline and demographic characteristics were balanced across the 2 study arms of interest for this review (except for age), suggesting that randomization was successful. The open-label design was the key limitation of the CLEAR trial because it increased the risk of assessment and reporting bias, especially for subjective outcomes such as HRQoL and safety. The primary outcome (PFS) and secondary outcomes (ORR, DOR, and DCR) were assessed by an IIR team using the RECIST 1.1 criteria, thus minimizing assessment bias. The time-to-event outcomes (OS, PFS) and other secondary outcomes (ORR, DOR, DCR, HRQoL, and safety) investigated in the trial were considered clinically meaningful by the clinician experts and reflective of outcomes assessed in clinical practice. The magnitude of

effect of LEN-PEM on HRQoL is uncertain because of potential bias in reporting and attrition (rates of completion of questionnaires were less than 50% at cycle 26 for the LEN-PEM arm and cycle 12 for the SUN arm). The concomitant medications permitted (including subsequent anticancer therapies permitted in the follow-up phase) were also considered appropriate by the clinician experts and reflective of treatments used in Canadian practice. Several interim analyses and subgroup analyses were pre-specified in the protocol before the third interim data cut-off (August 28, 2020). The final OS analysis will take place after approximately 304 deaths are observed in the LEN-PEM and SUN arm. Adjustments were made to account for alpha spending during the interim analysis. Multiplicity adjustments were implemented adequately for the analysis of PFS, OS, and ORR, and sensitivity analyses were also conducted for PFS. The findings from the sensitivity analyses were consistent with the primary ITT analyses. No multiplicity adjustments were made during the analysis for DOR, DCR, HRQoL, and the defined subgroups; thus, the findings were considered exploratory. The study was considered adequately powered to detect differences in PFS between the LEN-PEM arm versus the SUN arm. The threshold margins defined by the sponsor for PFS, OS, and ORR were considered clinically significant by the clinician experts consulted.

The clinician experts consulted considered the baseline characteristics and the findings of the CLEAR trial generalizable to adult patients with untreated advanced or metastatic RCC with a clear cell component in the Canadian setting. The dosage of LEN and PEM used in the trial aligns with the Health Canada indication. SUN was considered an appropriate comparator. The experts noted that treatment options such as AXI-PEM were not available in practice for patients at the time of the trial initiation. SUN was the standard-of-care option for untreated RCC patients with advanced or metastatic disease in Canada. According to the clinician experts consulted, patients with brain metastases who have had received prior treatment for brain metastasis can benefit from, and are eligible to receive treatment with, LEN-PEM except in cases of uncontrolled disease. Patients recruited in the CLEAR trial had better access to disease assessments and follow-up procedures compared with patients in real-world practice. The frequency of disease assessments and follow-up procedures in the CLEAR trial were considered appropriate by the clinician experts.

Indirect Comparisons

Description of Studies

One NMA submitted by the sponsor and 4 published ITCs identified in the literature were summarized for this review. The objectives of the sponsor-submitted NMA and published ITCs were to assess the comparative clinical efficacy and/or safety of LEN-PEM compared with other first-line treatments for advanced RCC based on evidence from randomized controlled trials (RCTs).

The network informing the NMA submitted by the sponsor comprised 24 phase II and phase III RCTs. The trials included adults with advanced or metastatic RCC who received first-line systemic treatments for advanced or metastatic RCC administered alone or in combination, best supportive care, or placebo. The studies enrolled patients between 1992 and 2019, and the study sample sizes ranged from 101 patients to 1,110 patients. A total of 18 studies reported on the timing of response assessments, which varied across studies from every 6 weeks to every 12 weeks. Among the 24 trials, median ages of the study populations ranged from 55 years to 68 years. Patients were described by risk category using the MSKCC criteria (16 studies), IMDC criteria (5 studies), or both (2 studies). If baseline risk was reported (in 23 of 24 studies), 23.5% to 81% of patients in each treatment group were intermediate risk. In

most of the studies included in the network (21 studies), the majority of patients had either a Karnofsky score of at least 70 or an ECOG score of 0 or 1 (4 studies included less than 13% of patients with an ECOG score of 2 and 1 study included 80% to 83% of patients with a Karnofsky score of 70 or less). In all studies that reported information regarding histology (21 studies), the most common histological RCC subtype was clear cell, with at least 78% of patients possessing clear cell or predominantly clear cell histology.

The studies included in the published ITCs were also included in the sponsor-submitted NMA. The methodology used for the published ITCs lacked important details, which hindered the ability to appropriately interpret the reported results. Further, individual estimates of treatment effects for the indirect comparisons involving LEN-PEM with other combination therapies were not reported for any outcomes. The NMA submitted by the sponsor was the most comprehensive assessment of indirect evidence among these studies, and it will be described subsequently. The published ITCs were considered supportive of the sponsor-submitted NMA.

Efficacy Results

Progression-Free Survival

The base-case analysis of PFS (with FDA censoring) used a random-effects model and included 18 comparators from 21 RCTs. The reported HR for LEN-PEM compared with the following comparators was 0.44 (95% credible interval [CrI], 0.23 to 0.82) versus nivolumab plus ipilimumab, 0.57 (95% CrI, 0.31 to 1.08) versus AXI-PEM, and 0.38 (0.21 to 0.67) versus pazopanib. The author indicated that the point estimates of the fixed-effect model were similar to the random-effects model, although the CrIs were narrower [redacted] For PFS, based on an random-effects model, LEN-PEM showed benefit compared with nivolumab plus ipilimumab and pazopanib. The random-effects model did not show a difference for the comparison with AXI-PEM, whereas the results for the fixed-effect model favoured LEN-PEM.

Overall Response Rate

The base-case analysis of ORR used a fixed-effect model and included 13 comparators from 14 RCTs. The OR for LEN-PEM compared with nivolumab plus ipilimumab was 3.24 (95% CrI, 2.18 to 4.85), AXI-PEM was 1.86 (95% CrI, 1.23 to 2.84), and pazopanib was 3.00 (95% CrI, 2.02 to 4.47). The author reported that the CrIs were larger in the random-effects model, which only affected the comparison with AXI-PEM [redacted]. Similar to the results for PFS, the results of the analysis of ORR based on a fixed-effect model showed a benefit of LEN-PEM when compared with other treatments.

Overall Survival

The base-case analysis of OS was performed using a fixed-effect model only and included 13 comparators from 12 RCTs. The HR for comparisons of LEN-PEM to nivolumab plus ipilimumab was 1.04 (95% CrI, 0.77 to 1.42), AXI-PEM was 0.99 (95% CrI, 0.71 to 1.37), and pazopanib was 0.78 (95% CrI, 0.58 to 1.06). These results suggest that the analysis of OS did not show a difference for LEN-PEM compared with other treatments.

Harms Results

All-Cause AEs of Grade 3 and Higher

[redacted]

[redacted]

Treatment Discontinuation Due to an AE

[redacted]

Critical Appraisal

The methodology used for the study selection in the systematic literature review was pre-specified and used an appropriate set of criteria in terms of the study characteristics for a systematic review, databases searched, data extraction process, and quality assessment. The literature review was comprehensive and was expected to have captured the relevant studies of interest. Despite an inclusive literature search, most of the connections within the network were limited to 1 study. Comparisons of interest (due to their relevance in the Canadian treatment setting) within the network were limited to indirect estimates only and were based on 1 open-label RCT; therefore, inconsistency could not be assessed in these connections. Based on a qualitative review of the populations of included studies, there were some concerns regarding potential bias due to effect modifiers. This included some differences between study populations in terms of number of metastases, prior nephrectomy, presence of sarcomatoid features, and distribution of patients by risk status, which may warrant further review. This remains a source of uncertainty in the network. The quality of included studies was assessed using the Cochrane Risk of Bias Assessment Tool 2.0, but information about the results of the quality assessment of individual studies was not reported. Additionally, information about study withdrawal or dropouts were not reported, which limits the ability to evaluate the internal validity of included studies.

The clinical experts consulted by CADTH indicated that the sponsor-submitted NMA considered all relevant comparators in the Canadian context. Information about the dosing of treatments included in all trials within the network was limited, with details regarding relative dose intensity, compliance, or missed dosing not reported or poorly reported. Efficacy and safety outcomes included in the NMA were clinically relevant, but HRQoL was not included, which was a limitation of the sponsor-submitted NMA. Some of the patient characteristics were inconsistently reported across trials; in particular, details about race and ethnicity, PD-L1 status, and cancer staging were infrequently reported. In general, heterogeneity was identified as a limitation without adjustment, although some subgroup or sensitivity analyses were performed. Subgroup analyses were limited by sample size (patients in the poor and favourable risk subgroups represented a small proportion of patients in the overall population). Overall, interpretation of the results for subgroup analyses of the NMA is limited.

Differences in time point assessments and actual treatment duration were also acknowledged as a limitation of the NMA, as well as the effect caused by immature data for efficacy assessments. A sensitivity analysis was conducted in which trials with a follow-up period of less than 12 months were excluded; however, no adjustments were made for the variation in follow-up duration for studies with durations greater than 12 months. For reference, in the CLEAR trial, the analysis of OS was based on data with a median follow-up of approximately 33 to 34 months, and the analysis of PFS was based on a median follow-up of 26 to 27 months. The results for OS and PFS were based on a median follow-up of 43 months

in the KEYNOTE-426 trial, and a minimum of 48 months in the CheckMate-214 trial. The effect of this heterogeneity in duration of follow-up has on these outcomes is unknown.

The sponsor-submitted ITC included justification of model selection (fixed effect vs. random effects) based on assessment of model fit or a lower deviance information criterion, although reported differences were very small. Assessments of heterogeneity based on I^2 and inconsistency were also considered, although most connections were formed by a single RCT and there were few closed loops. The random-effects model used an informative prior before stabilize estimates of between-study variance. The prior was based on plausible values, and sensitivity analyses were conducted. There was uncertainty in the results, with wide CrIs. This is likely due to the sparsity of the network. The results for the ORR had very wide CrIs, and the results for OS and all-cause AEs of grade 3 or higher included CrIs that crossed 1 and included values suggesting strong treatment effect, which limited interpretation of these results. The analysis of treatment discontinuation due to AEs was also associated with imprecision and uncertainty from wide CrIs that crossed 1, while also including values suggesting strong treatment effect, although the fixed-effect model improved precision.

Conclusions

One pivotal study and 5 ITCs provided evidence for the CADTH systematic review. This review focused on the comparison between LEN-PEM and SUN investigated in the CLEAR trial as per the sponsor's reimbursement request and the Health Canada indication. No other evidence directly comparing LEN-PEM to other standard therapies for advanced or metastatic RCC was identified. In the CLEAR trial, the median PFS estimated by IIR at the final interim analysis for PFS (August 28, 2020) was 23.9 months in patients receiving LEN-PEM compared with 9.2 months in patients receiving SUN. The HR estimated for PFS between LEN-PEM and SUN was considered statistically and clinically significant. The median OS was not estimable in both study arms at the interim 3 data cut-off or at the follow-up analysis on March 31, 2021. However, the HR estimated between LEN-PEM and SUN was considered statistically significant. The ORR estimated in the LEN-PEM arm was also considered statistically significant. The HRQoL assessments were considered exploratory due to the lack of multiplicity adjustments in the analysis and the potential for reporting bias. The findings of the CLEAR trial were considered by the clinician experts consulted during the review to be meaningful for patients with advanced or metastatic RCC and were aligned with outcomes of importance to patients. In the opinion of the clinician experts, clinical judgment is required to evaluate the clinical benefit of LEN-PEM's and the management of AEs in practice. The experts anticipate that the treatment-related AEs resulting from the use of LEN-PEM will be managed in practice using similar strategies already in place for other treatment options (frequent AE monitoring, dose adjustments, reductions and modifications that are anticipated for the treatment). The open-label design was a key limitation of the CLEAR trial, and the OS data are interim. The study was randomized, and adjustments for multiplicity were conducted for key outcomes (PFS, OS, and ORR) which minimized bias in the study. The clinician experts considered the baseline characteristics and the findings from the CLEAR trial generalizable to patients diagnosed with advanced or metastatic RCC in the first-line setting in Canada.

No direct evidence was available to assess the relative efficacy of LEN-PEM versus other current standard-of-care therapies. Indirect evidence for LEN-PEM as a first-line treatment for patients with advanced or metastatic RCC was available based on 5 ITCs: 1 NMA submitted by the sponsor and 4 ITCs identified in the published literature. The sponsor-submitted NMA of LEN-PEM compared with other available therapies showed benefit of LEN-PEM for PFS and ORR, but not OS, compared with other therapies. Sources of uncertainty identified during

the review included heterogeneity in the RCTs, sparse network, and lack of data maturity (shorter follow-up duration) for the CLEAR trial. The sponsor-submitted NMA results of the analysis of treatment discontinuation due to AEs [redacted], although these results were limited by a lack of precision plus a number of assumptions made about the outcome that caused uncertainty in the results. Findings on OS, PFS, and ORR obtained from 4 additional published ITCs assessed in this review were consistent with the results of the sponsor-submitted NMA. However, the methodology used for the analyses lacked important details, which hindered the ability to appropriately interpret the reported results.

Economic Evidence

Table 3: Cost and Cost-Effectiveness

Component	Description
Type of economic evaluation	Cost-utility analysis Partitioned survival model
Target populations	Base case 1: Treatment of adult patients with advanced (not amenable to curative surgery or radiation) or metastatic RCC with no prior systemic therapy for metastatic RCC or metastatic RCC with no prior systemic therapy for metastatic RCC regardless of IMDC risk status (Health Canada indication). Base case 2: Treatment of adult patients with advanced or metastatic RCC with no prior systemic therapy for metastatic RCC who are intermediate/poor risk as per IMDC.
Treatments	Lenvatinib in combination with pembrolizumab (LEN-PEM)
Submitted price	LEN 8 mg dose (two 4 mg capsules): $68.64 per day LEN, 10 mg, dose (one 10 mg capsule): $75.28 per day LEN 14 mg dose (one 10 mg capsule + one 4 mg capsule): $116.93 per day LEN 20 mg dose (two 10 mg capsules): $175.41 per day
Treatment cost	At the sponsor's submitted price of $175.4127 per 20 mg dose, the cost per 21-day cycle of LEN is $3,864.00. At a price of $4,400 per 100 mg vial, the cost of PEM per 21-day cycle is $8,800. Together, the total 21-day cycle cost for LEN-PEM is $12,484 or $216,978 annually if patients remain on treatment for a full year.
Comparators	Base case 1: AXI-PEM, SUN, and PAZO Base case 2: AXI-PEM, SUN, PAZO, and NIVO-IPI
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime (30 years)
Key data source	CLEAR (Study 307), a phase III, randomized, open-label trial (LEN-PEM vs. SUN), and sponsor's conducted NMA (vs. AXI-PEM, PAZO, and NIVO-IPI)

Component	Description
Key limitations	• As a PSM assumes independence between PFS and OS, and because LEN-PEM was found to have superior PFS but similar OS to AXI-PEM, this led to pre-progression survival benefits for LEN-PEM and post-progression survival benefits for AXI-PEM that are not clinically expected. • The clinical parameters for the intermediate/poor risk subgroup analysis were uncertain because the CLEAR trial did not consider the intermediate/poor risk groups together. Additionally, the CADTH clinical report concluded that the subgroup analysis results are uncertain and should be hypothesis-generating only. • There is no evidence of long-term PFS with LEN-PEM (duration of evidence for PFS = 38 months), and predicting PFS outcomes beyond 20 years was noted to be speculative by the clinical experts. • The sponsor's TTD extrapolations for LEN assumed a longer time between treatment discontinuation and progression than expected by the clinical experts, which resulted in an underestimation of LEN costs. The proportion of patients who received subsequent therapies upon progression was higher than expected in Canadian clinical practice. • The sponsor assumed a shorter duration of treatment with subsequent therapies following first-line treatment with LEN-PEM compared to all other comparators, which is not expected according to the clinical experts. • The sponsor's approach to estimating LEN drug costs included a dose-weighted average per patient, which could not be validated by CADTH. Additionally, nonlinear pricing was incorporated such that two 10 mg doses would cost less than a 20 mg LEN dose. The costs of LEN were therefore uncertain. • The sponsor applied RDI in the derivation of the costs for LEN, PEM (for LEN-PEM only), SUN, and PAZO. This is inappropriate because RDI can be influenced by many different factors. • The costs of managing anemia and hypertension AEs were considered to be overestimated by clinical experts.
CADTH reanalysis results	• CADTH undertook reanalyses to address limitations relating to uncertainty in long-term PFS for treatment with LEN-PEM, aligning LEN TTD with CLEAR trial observations and ensuring DOT is close to but not greater than PFS, assuming DOT for subsequent therapies was equal for all comparators, assuming 50% of patients receive subsequent therapy upon progression, assuming an RDI of 100% for all treatments, and adjusting AE treatment costs for anemia and hypertension to reflect the outpatient nature of their management. • In the CADTH base case, for the proposed Health Canada–indicated population, LEN-PEM was associated with an ICER of $667,600 compared to AXI-PEM (incremental costs = $78,851; incremental QALYs = 0.12). More than 40% of probabilistic model results found incremental QALYs < 0.0, suggesting a very high degree of uncertainty around the comparative effectiveness of these 2 treatments. • For LEN-PEM to be cost-effective compared to AXI-PEM at a willingness-to-pay threshold of $50,000 per QALY, a 56% reduction in the price of LEN is required. • Even at a 100% reduction in the price of LEN, LEN-PEM has an ICER of $96,922 vs. PAZO. A further 29% reduction in the price of PEM would be needed for LEN-PEM to be cost-effective compared with PAZO at the $50,000 per QALY threshold.

AXI = axitinib; ICER = incremental cost-effectiveness ratio; IMDC = International mRCC Database Consortium; IPI = ipilimumab; LEN = lenvatinib; LYs = life-years; NMA = network meta-analysis; NIVO = nivolumab; OS = overall survival; PAZO = pazopanib; PEM = pembrolizumab; PFS = progression-free survival; PSM = partitioned survival model; QALY = quality-adjusted life-year; RCC = renal cell carcinoma; RDI = relative dose intensity; TTD = time to deterioration; vs. = versus.

Budget Impact

CADTH identified the following key limitations with the sponsor's analysis:

- The relative dosing intensities for all treatments were underestimated.
- The anticipated market uptake of LEN-PEM was overestimated.

- The market share distribution in the reference scenario did not reflect Canadian clinical practice.
- The duration of therapy for LEN-PEM and AXI-PEM were revised to reflect values in the CADTH pharmacoeconomic analysis.
- Limitations were identified with several inputs used to estimate the population size eligible for treatment with LEN-PEM, which likely underestimated the population size.

CADTH estimated a revised base case which included revising the relative dosing intensities for all treatments, revising the anticipated market uptake of LEN-PEM, revising the market share distribution in the reference scenario, and revising the duration of therapy.

Based on the CADTH reanalyses, the estimated budget impact from the reimbursement of LEN-PEM would be a cost savings of -$17,829,174 in year 1, and a budget increase of $18,633,975 in year 2 and $41,094,727 in year 3, for a total incremental budget impact of $41,899,528 over the 3-year time horizon.

CADTH was unable to address limitations related to the uncertainty around the estimated population size eligible for LEN-PEM. The budget impact is highly sensitive to changes in the estimated population size, as shown in scenario analyses assessing the proportion of patients with RCC assumed to receive first-line treatments and assessing the proportion of patients who were eligible to receive coverage.

pERC Information

Members of the Committee

Dr. Maureen Trudeau (Chair), Mr. Daryl Bell, Dr. Jennifer Bell, Dr. Matthew Cheung; Dr. Winson Cheung, Dr. Michael Crump, Dr. Leela John, Dr. Christian Kollmannsberger, Mr. Cameron Lane, Dr. Christopher Longo, Dr. Catherine Moltzan, Ms. Amy Peasgood, Dr. Anca Prica, Dr. Adam Raymakers, Dr. Patricia Tang, Dr. Marianne Taylor, and Dr. W. Dominika Wranik

Meeting date: April 12, 2022

Regrets: 2 expert committee members did not attend.

Conflicts of interest: None