CADTH

CADTH Reimbursement Review

CADTH Reimbursement Recommendation

(Draft)

Nivolumab and Relatlimab (Opdualag)
Indication: For the treatment of adult and pediatric patients 12 years of age or older with unresectable or metastatic melanoma who have not received prior systemic therapy for unresectable or metastatic melanoma

Sponsor: Bristol Myers Squibb Canada

Recommendation: Reimburse with Conditions

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Recommendation

The CADTH pCODR Expert Review Committee (pERC) recommends that nivolumab and relatlimab be reimbursed for the treatment of adult and pediatric patients 12 years of age or older with unresectable or metastatic melanoma who have not received prior systemic therapy for unresectable or metastatic melanoma only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

Evidence from one phase 2/3, double blinded, randomized, active controlled and ongoing trial (RELATIVITY-047) demonstrated that treatment with nivolumab and relatlimab fixed dose combination when compared with nivolumab monotherapy resulted in added clinical benefit in patients with previously untreated, histologically confirmed unresectable stage III or stage IV (metastatic) melanoma. Nivolumab and relatlimab was associated with a statistically significant and clinically important increase in progression-free survival (PFS) benefit when compared with nivolumab monotherapy (primary analysis, median follow-up of 13.2 months, hazard ratio [HR]: 0.75, 95% CI 0.62 to 0.92; p=0.0055). Nivolumab and relatlimab may result in a clinically important increase in OS when compared with nivolumab monotherapy (HR 0.80 [95% CI 0.64 to 1.01]; p=0.0593). However, there remains uncertainty in the OS results due to the inadequate length of follow up for this outcome and the 95% confidence interval included no difference between the nivolumab plus relatlimab and nivolumab monotherapy. Based on descriptive final analyses, a total of 10.3% (95% CI: 3.4 % to 17.3%) more patients in the nivolumab and relatlimab group achieved an objective response (OR) compared with the nivolumab group after a median follow up of 19.3 months. After a median follow-up of 19.3 months, HRQoL (FACT-M, EQ-5D-3L utility index scores and EQ-5D-VAS) in the nivolumab and relatlimab and nivolumab groups remained generally stable (no clinical meaningful improvement or deterioration) during the treatment period. There were little to no differences between nivolumab and relatlimab and nivolumab monotherapy in FACT-M, EQ-5D-3L utility index scores, and EQ-5D-VAS.

Despite the available treatment options, there remains an unmet therapeutic need for effective treatment options for patients with unresectable or metastatic melanoma. Patient groups indicated that there is an ongoing need for better options with fewer adverse events and longer responses as well as the need to have available treatment options when one therapy does not work or stops working. Nivolumab and relatlimab compared to nivolumab monotherapy was effective with respect to PFS. While there were numerically more patients who experienced adverse events (e.g., grade 3 or 4 adverse events) in the nivolumab and relatlimab group than in the nivolumab monotherapy group, the adverse events were generally manageable.

At the sponsor submitted price for nivolumab and relatlimab and publicly listed prices for immunotherapies considered in the submitted indirect treatment comparison (nivolumab and ipilimumab combination, pembrolizumab, ipilimumab, and nivolumab monotherapy) nivolumab and relatlimab was more costly than nivolumab and ipilimumab combination, pembrolizumab, ipilimumab, and nivolumab monotherapy. As there was insufficient evidence to conclude that nivolumab and relatlimab is as effective or better than nivolumab and ipilimumab combination to justify a cost premium, the total drug cost of nivolumab and relatlimab should not exceed the total drug cost of nivolumab and ipilimumab combination.

Table 1. Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Treatment with nivolumab and relatlimab fixed dose combination (FDC) should be reimbursed only in patients with all of the following characteristics: 1.1. Histologically confirmed unresectable stage III or stage IV (metastatic) melanoma 1.2. Have not received prior systemic therapy for unresectable or metastatic melanoma 1.3. Aged 12 years or older 1.4. Good performance status	Evidence from the RELATIVITY-047 study demonstrated that treatment with nivolumab and relatlimab fixed dose combination when compared with nivolumab monotherapy resulted in added clinical benefit in patients with previously untreated, histologically confirmed unresectable stage III or stage IV (metastatic) melanoma. These conditions are reflective of the patients enrolled in the RELATIVITY-047 study.	
2. Treatment with nivolumab and relatlimab FDC could be reimbursed in patients who had prior adjuvant or neoadjuvant anti-PD-1 or anti-CTLA-4 therapy if the therapy was completed at least 6 months before the date of recurrence.	As per eligibility criteria for RELATIVITY-47, prior adjuvant or neoadjuvant anti-PD-1 or anti-CTLA-4 therapy was allowed if all related AEs had returned to baseline or stabilized, provided that prior adjuvant or neoadjuvant anti-PD-1 or anti-CTLA-4 therapy was completed at least 6 months before the date of recurrence.	
3. Treatment with the nivolumab and relatlimab FDC should not be reimbursed in patients with: 3.1. Active brain metastases 3.2. Uveal melanoma 3.3. Active autoimmune disease	Patients with these conditions were excluded from the RELATIVITY-047 trial. As a result, there was no evidence reviewed for patients with active brain metastases, uveal melanoma, and active autoimmune disease.	
Renewal		
4. Treatment with nivolumab and relatlimab FDC may continue unless any of the following occurs: 4.1. Clinical or radiographic disease progression 4.2. Intolerable side effects that cannot be managed by dose interruption	These conditions are reflective of the intervention and discontinuation criteria in the RELATIVITY-047 trial and/or the clinical experts' input.	
5. Patients should be assessed for a response to treatment with nivolumab and relatlimab FDC	In the RELATIVITY-047 trial, tumour assessments began 12 weeks from randomization and continued every 8 weeks up to week 52, and every 12 weeks	

Reimbursement condition	Reason	Implementation guidance
every 2 to 3 months initially and then as per standard of care.	thereafter until BICR-confirmed disease progression or treatment discontinuation, whichever occurred later. According to clinical experts, initial response assessment at 3-month intervals, and as the patient responds, the response assessment can be tailored with increased interval over time.	
Discontinuation		
6. Treatment with nivolumab and relatlimab FDC should be discontinued upon the occurrence of any of the following: 6.1. Clinical or radiographic disease progression 6.2. Unacceptable toxicity	These conditions are reflective of the intervention and discontinuation criteria in the RELATIVITY-047 trial as well as the clinical experts' input.	
Prescribing		
7. Nivolumab and relatlimab FDC should only be prescribed by clinicians who: 7.1. Have expertise in diagnosis and management of patients with melanoma 7.2. Are familiar with the toxicity profile associated with nivolumab and relatlimab FDC	To ensure that the nivolumab and relatlimab FDC is prescribed only for appropriate patients and that patients receive optimal care for toxicity management.	
Pricing		
8. A reduction in price	Given the uncertainty in the relative efficacy of nivolumab and relatlimab compared to nivolumab and ipilimumab, the total drug cost of nivolumab and relatlimab should not exceed the total drug cost of nivolumab and ipilimumab. Given the potential that nivolumab and relatlimab would not be considered equally efficacious to nivolumab and ipilimumab, a further price reduction to achieve cost savings may be warranted.	
9. The feasibility of adoption of nivolumab and relatlimab must be addressed	At the submitted price, the magnitude of uncertainty in the budget impact must be addressed to ensure the feasibility of adoption, given the difference between the	

Reimbursement condition	Reason	Implementation guidance
	sponsor's estimate and CADTH's estimate(s).	

Discussion Points

- pERC discussed the current treatment options available to patients and noted that treatment is dependent on BRAF mutation status. First line treatment options include immune checkpoint inhibitor (ICI) monotherapy (pembrolizumab, nivolumab, ipilimumab), ICI combination therapy (nivolumab and ipilimumab) and targeted BRAF therapy. Current standard first line therapy for patients with BRAF negative melanoma who are fit is nivolumab combined with ipilimumab, and for those who are less fit, single agent pembrolizumab or nivolumab. For BRAF mutation positive melanoma, patients can either receive the ICI combination first or BRAF directed therapy, and those who are less fit have access to single agent nivolumab or pembrolizumab. pERC acknowledged the input from the clinical experts which suggests nivolumab and ipilimumab combination as the preferred standard of care in the first line setting for patients who are young and healthy and willing to tolerate the adverse events associated with treatment, irrespective of BRAF mutation status.
- pERC discussed the possible place in therapy of nivolumab and relatlimab, and concluded that nivolumab and relatlimab would be another alternative treatment option for patients who are not fit enough to receive nivolumab and ipilimumab combination or for patients who are ipilimumab ineligible and would have otherwise receive nivolumab monotherapy, pembrolizumab monotherapy, or targeted BRAF therapy.
- Based on the direct evidence, while pERC was confident in the PFS benefit of nivolumab and relatlimab compared to nivolumab monotherapy, pERC was less confident in the OS benefit since these results were not statistically significant and longer length of follow up is needed to confirm an OS benefit.
- pERC acknowledged an established clinical benefit with nivolumab and ipilimumab combination for patients who are fit enough to endure the toxicities associated of this combination compared with nivolumab. While the RELATIVITY-047 study compared nivolumab and relatlimab to nivolumab monotherapy, there is no direct evidence to suggest a clinical benefit compared to nivolumab and ipilimumab combination. There remains uncertainty in the comparative efficacy of nivolumab and relatlimab compared to relevant comparators, including nivolumab and ipilimumab combination. pERC, however, acknowledged that according to clinical expert opinion, nivolumab and relatlimab has less toxicity than nivolumab and ipilimumab combination.
- While the sponsor-submitted ITCs to address this gap, the evidence from these comparisons was inconclusive due to inherent limitations (between trial differences, immature OS data, important outcomes such as ORR and TTP were not included). As a result, there is insufficient evidence to support a conclusion that nivolumab and relatlimab provides additional or similar benefit to that provided by nivolumab and ipilimumab. Consequently, pERC concluded that the evidence may support the conclusion that the total drug cost of nivolumab and relatlimab should be lower than the total drug cost of nivolumab and ipilimumab.
- pERC discussed the uncertainty present in the budget impact analysis. pERC recognized that the choice of first line therapy will be determined by patient preference, fitness and willingness to endure toxicity and discussions between clinician and patient, which is consistent with clinical expert opinion. Clinical experts suggested that given the number of efficacious treatments available for melanoma in the unresectable, metastatic setting, it was difficult to estimate the likely change in prescribing patterns that might result if nivolumab and relatlimab were reimbursed. The reimbursement of first line nivolumab and relatlimab is also likely to have implications on prescribing patterns for second-line therapies that are difficult to predict. This uncertainty in the market share of different treatments (and therefore the overall assessment of budget impact) may present challenges for the feasibility of adoption for this reimbursement recommendation.

Background

Melanoma is a neoplasm originating from melanocytes or the pigment-producing cells of the skin. The clinical symptoms of advanced melanoma include swollen lymph nodes, hard lump on your skin, unexplained pain, feeling very tired or unwell, unexplained weight loss etc. The mean age at diagnosis of advanced metastatic melanoma is approximately 59 years in Canada. The diagnosis of melanoma is based on skin examination, physical examination, skin and/or lymph node biopsy, and diagnostic imaging (i.e., computed tomography). According to the Canadian Cancer Society, 10.4% of all new melanomas are stage III at diagnosis and 3.9% are stage IV (i.e., metastatic disease). Poor prognostic factors include Eastern Cooperative Oncology Group (ECOG) performance status ≥2, elevated lactate dehydrogenase (LDH), nodal involvement and metastases, increased tumor thickness, ulceration, and mitoses ≥1/mm2 in thin T1 melanomas. Approximately 70% of metastatic melanomas have mutually exclusive mutations in B-Raf proto-oncogene (BRAF), neuroblastoma RAS viral oncogene homolog (NRAS) gene (NRAS), c-KIT, and GNAQ or GNA11, which activate the mitogen-activated protein kinase (MAP kinase, MAPK) pathway leading to promotion of cell proliferation, prevention of apoptosis, and angiogenesis. About 38 % to 51% of patients with stage III or IV melanoma had a mutation in the BRAF gene. An Australian study of patients with advanced melanoma reported a similar rate, with 48% of tumors being BRAF V600-mutation positive. In Canada, melanoma accounted for 3.8% of new cancer cases and 1.5% of cancer deaths in 2021.12 An estimated 9,000 people were diagnosed with melanoma in 2022 in Canada, with an age-standardized incidence rate of 23.5 per 100,000 in 2018 (excluding Québec) based on data from Statistics Canada. Incidence is slightly higher in men than in women (25.9 versus 21.2 per 100,000). An estimated 1,200 persons died from melanoma in 2022 in Canada, with an age-standardized mortality rate of 2.7 per 100,000. In Canada, stage IV distant metastatic disease is associated with a 5-year survival rate of 18%.4 However, consistent with the observed decline in mortality rates, melanoma survival rates have improved in recent years with the introduction of novel immunotherapies and BRAF-targeted therapies (TT) with BRAF and MEK inhibitors.

Important treatment goals of systemic therapy in metastatic advanced melanoma include: prolonging survival, generating durable responses, providing symptom relief, minimizing treatment toxicities, and maintaining quality of life. According to the clinical experts CADTH consulted for this review, immunotherapy is the first line of choice for melanoma regardless BRAF status. The immune checkpoint inhibitor (ICI) immunotherapies routinely used for the first-line treatment of metastatic melanoma in Canada includes ipilimumab plus nivolumab combination therapy, nivolumab (anti-PD-1) monotherapy, ipilimumab (anti-CTLA-4) monotherapy, and pembrolizumab (anti-PD-1) monotherapy. However, the use of nivolumab plus ipilimumab (NIVO+IPI) has been increasing. According to the clinical experts CADTH consulted for this review, NIVO+IPI is the first line of choice among the ICIs. After the first line, the treatment decisions are largely determined by BRAF mutation status. Patients with no BRAF mutation are treated with immunotherapies and patients with BRAF mutations are eligible for treatment with TT. TT regimens have been approved by Health Canada and recommended for reimbursement by pERC includes encorafenib (BRAF inhibitor) plus binimetinib (MEK inhibitor), vemurafenib (BRAF inhibitor) plus cobimetinib (MEK inhibitor), and dabrafenib (BRAF inhibitor) plus trametinib (MEK inhibitor). The clinical experts CADTH consulted for this review indicated that TT use as monotherapies is negligible and not reflective of clinical practice in Canada. It was reported that patients with advanced melanoma rarely receive TT as a single agent (<5%). According to the clinical experts CADTH consulted for this review, there is an unmet medical need for an additional novel ICI combination therapy in metastatic melanoma which can be used regardless of BRAF mutation status. The novel therapy should offer increased efficacy in relation to anti-PD-1 monotherapy and should have a favorable safety profile that does not result in additive toxicities as seen with conventional dual immunotherapy combinations - a combination treatment regimen involving an ICI combined with a drug with a different mechanism of action.

Nivolumab is a humanized IgG4 monoclonal antibody (mAb) immune checkpoint inhibitor (ICI) that binds to the programmed death (PD)-1 receptor and blocks its interaction with PD-L1 and PD-L2, releasing PD-1 pathway-mediated inhibition of the immune response, including the anti-tumor immune response. Relatlimab is a novel, first-in-class ICI that targets the lymphocyte activation gene-3 (LAG-3) receptor. Relatlimab is a humanized IgG4 mAb that binds to the LAG-3 receptor and prevents LAG-3-mediated inhibition of the immune response by blocking its interaction with ligands, ultimately leading to an anti-tumor response. LAG-3 and PD-1 are two distinct inhibitory immune checkpoint pathways, often co-expressed on tumor-infiltrating lymphocytes. They act synergistically on effector T-cells, leading to the development of T-cell exhaustion and impaired cytotoxic function. The recommended dose of nivolumab plus relatlimab are: for adult patients: 480 mg nivolumab and 160 mg relatlimab, Q4W;

The recommended Opdualag dosage for pediatric patients who are at least 12 years old and weigh at least 40 kg is the same as for adults. A recommended dose has not been established for pediatric patients who are 12 years or older and weigh less than 40 kg. Nivolumab plus relatlimab is supplied as concentrate for solution for infusion: 240 mg of nivolumab per 20 mL (12 mg/mL) and 80 mg of relatlimab per 20 mL (4 mg/mL) in a single-dose vial (fixed dose combination [FDC]).

The Health Canada approved indication of interest for this review is nivolumab plus relatlimab FDC (NIVO+RELA FDC) for the treatment of adult and pediatric patients 12 years of age or older with unresectable or metastatic melanoma who have not received prior systemic therapy for unresectable or metastatic melanoma. The CADTH reimbursement request aligns with this Health Canada indication. The NIVO+RELA FDC was reviewed by Health Canada through the Standard Review Pathway. It has not been reviewed previously by CADTH.

Sources of Information Used by the Committee

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

- a review of one phase 2/3, double blinded, randomized controlled and ongoing trial (the RELATIVITY-047, N=714) randomized controlled trial in patients with previously untreated, unresectable, or metastatic melanoma
- patient perspectives gathered by two patient groups, Melanoma Canada and Save Your Skin Foundation (SYSF)
- input from public drug plans and cancer agencies that participate in the CADTH review process
- two of clinical specialists with expertise diagnosing and treating patients with melanoma
- input from one clinician group, Ontario Health (Cancer Care Ontario) Skin Cancer Drug Advisory Committee (OH-CCO's Drug Advisory Committees)
- a review of the pharmacoeconomic model and report and indirect treatment comparisons submitted by the sponsor

Stakeholder Perspectives

Patient Input

CADTH received two patient group submissions from Melanoma Canada and Save Your Skin Foundation (SYSF). Data was gathered by Melanoma Canada via an on-line survey. A total of 119 individual patient responses combined with 84 caregiver responses were received. 35 patient respondents indicated they had no caregiver. Of the total responses for patients, 81 were female and 38 were male. There were 26 patients that were stage 0; 17 were stage I; 10 were stage II; 18 were stage III; 29 were stage IV and a further 19 did not know their stage. Two patients in this survey were treated with nivolumab plus relatlimab FDC.

Information was obtained by SYSF through online surveys, virtual patient roundtables and one-on-one conversations, which included 60 melanoma patients of 12 on the drug under review (nivolumab plus relatlimab) and was gathered over the past 6 months. There were 37 females and 23 males aged between 18 and 89 years old. A total of 18 (out of 60) respondents were from outside of Canada (USA, Australia, France).

Most patients reported that pain, scarring, lymphedema, fatigue, anxiety, fear and depression are common impacts of the disease itself that affect the quality of life for patients and their families; furthermore, caregivers reported that the biggest impact on them of dealing with the diagnosis is the mental stress, followed by the negative financial impact to the family with the loss of income from a working partner, and as well, the additional responsibilities that they have to perform for the home and family and to care for their loved one. Some of the respondents explained the impact of melanoma using the following phrases: scared, disbelief, unsettled, anxious, teary, disrupted life and totally life changing.

In terms of current therapy options, based on 119 of the respondents from Melanoma Canada's survey, 55% of respondents had been treated with some form of drug therapy. There were 9 patients who were treated with multiple therapies. A total of 92% of patients treated with available drug therapies indicated that they felt the side effects were worth it for the anticipated results.

Moreover, about 20% of patients experienced issues in accessing treatment. SYSF's survey also mentioned the same issues as patients in remote areas of Canada have problems getting to treatment if needed, travel costs and time off from work puts extra stress on patients and caregivers, huge expenses and increased stress to themselves and their family and the added concern of being treated far from home and their support system. There was very little access to the drug under review (ON and QC only) and there were a number of Canadian patients that could not get access to the drug under review which might have been their only option.

Regarding the improved outcomes, both patient groups identified that there is a vast opportunity for improvement with a wider variety of more effective treatment options with minimal side effects and longer response being made available.

There are two respondents from Melanoma Canada's survey and 12 respondents from SYSF's survey indicated that they had experience with the drug under review and the primary method of access to the drug under review was through clinical trial. There were 12 respondents who explained that benefits outweighed the experience of side effects which were mainly rash and fatigue and were somewhat manageable.

Melanoma Canada believes that there is an ongoing need for better options, and options when one therapy does not work or stops working. Melanoma Canada also noted that melanoma is very difficult to treat once it has spread. Effective treatments, biomarkers and earlier stage treatments are needed to prevent some of the quality-of-life impacts from surgery, loss of income, duration of illness and the impact on mental health for the patient and caregiver. According to Melanoma Canada, the drug under review is another improvement and option in a cancer that continues to be on the rise and is complex to treat.

Clinician Input

The following input was provided by 2 clinical specialists with expertise in the diagnosis and management of adult and pediatric patients (12 years and older and weighing at least 40 kg) with unresectable or metastatic melanoma.

The clinical experts indicated that the goal is to increase overall rates, to slow down progression, improve symptoms, improve quality and quantity of life and to minimize toxicity, especially long- term significant toxicities. The clinical experts indicated that formulations are needed to improve convenience. Currently the standard of care for metastatic melanoma in Ontario is ipilimumab plus nivolumab (IPI + NIVO), if the patient is able to tolerate the drugs with regards to potential toxicities. Failure to respond to ipilimumab plus nivolumab leads to potentially switching to BRAFi + MEKi in BRAF positive patients. Pembrolizumab may be attempted as monotherapy or Nivolumab as monotherapy if a patient experiences too many adverse events (AEs) due to IPI+NIVO combination treatment. The clinical experts indicated that immunotherapy is not 100% effective. The response rates of combination ipilimumab plus nivolumab is around 56%. Patients may initially get a response and then progress eventually. After progression, new treatments are needed. Moreover, sometimes treatments are effective, but the AEs are not tolerable and thus treatment has to be aborted despite efficacy and so less toxic treatments that are more easily tolerable and less dangerous is needed. This is an unmet need. According to the clinical experts, there is no real beneficial second line therapy better than ipilimumab plus nivolumab right now. New therapy is needed to increase response rate with fewer AEs. Furthermore, currently the standard practice, according to the clinical experts, would be to discuss dual agents versus single agent immunotherapy if no contraindications with their patients. Factors that would be considered in determining the most suitable treatment include: patient goals, age, comorbidities, bulk of disease, sites of disease, and pace of disease. If the patient elected dual agent therapy, they may de-escalate to single agent for toxicity management. If the patient progresses on dual therapy and has BRAF mutation, BRAF/MEK inhibitors would be offered. According to the clinical expert, dual immunotherapy has been recognized as potentially curable regimen. In addition, many trials are based on fixed dosing & limited vial sizes. The clinical experts noted that many provinces reimburse these therapies based on weight and that clinics are challenged to cohort patients to minimize drug wastage.

One clinical expert indicated that given its equivalency to ipilimumab plus nivolumab and fewer toxicities, the clinical expert consider the new treatment (NIVO+RELA FDC) under review as first line treatment for patients. The clinical experts highlighted that fewer AEs may mean more patient compliance and thus, better outcomes overall, and that less toxicity may mean fewer hospital admissions which overall is better for patients but also more economically sound and would offset the extra cost of the drug. Nivolumab plus relatlimab FDC could also be an alternative to ipilimumab plus nivolumab which is currently first-line in Ontario. The other clinical expert indicated that if this regiment is approved, then the options would be discussed with patients, ipilimumab plus nivolumab

versus nivolumab plus relatlimab FDC, regarding OS, PFS, and toxicities. The clinical expert also noted that nivolumab plus relatlimab FDC is directly compared to nivolumab monotherapy in the RELATIVITY-047 trial; nivolumab plus relatlimab FDC is the 1st class drug; nivolumab plus relatlimab FDC may be used as 1st line, or 2nd line of ICIs; nivolumab plus relatlimab FDC would not be reserved for those patients who are intolerant, but rather would benefit from an effective regimen with less toxicities; nivolumab plus relatlimab FDC is expected to cause a shift in treatment paradigms; those receiving candidates for single agent immunotherapy would be offered nivolumab plus relatlimab FDC; and those candidates considered for ipilimumab plus nivolumab may be offered or choose nivolumab plus relatlimab FDC. The clinical expert stated that this nivolumab plus relatlimab FDC regimen may replace ipilimumab plus nivolumab for less robust patients.

The clinical experts indicated that all metastatic patients can be offered this treatment as it was beneficial regardless of BRAF status, PDL-1 and LAG3 percentage or stage. It is similar to other immunotherapy combinations and thus could be offered to all patients. In addition, the experts also stated that it will be important: to follow OS data as it matures; to know the efficacy in brain metastases; and to know if the combination decreases or delays the occurrence of brain metastases.

As to the response assessment, the clinical experts indicated that it is needed to assess response by improved patient symptoms and the modified immunotherapy RESIST criteria as there can be pseudoprogression in the beginning of treatment. Usually, it can take up to 2-3 months to evaluate a true response. At the beginning, assessing the response at 3-month intervals for a while. As patients respond, the response assessment can be tailored and increased to every 6 months. Improved survival is the goal. The clinical experts noted that the clinical outcomes assessments are aligned with the clinical trial outcomes; physicians and patients review toxicities, symptom control and objective evidence of disease response in an ongoing fashion during active treatment.

Regarding discontinuation, the clinical experts indicated the nivolumab plus relatlimab FDC should be discontinued when obvious disease progression on imaging occurs, and with no improvement in symptoms. According to the clinical experts, when harmful grade 3-4 AEs occurs, patient should at the very least pause the treatment and start to treat the AE. Then, determine if the treatment can be restarted at a lower dose.

The clinical expert noted that treatments for metastatic melanoma should be provided by specialist medical oncologists and pharmacists in a Canadian Cancer Center or if at a Community Center then supervised or somehow connected to a cancer center and experts for advice. According to the clinical expert, a centre administering/managing patients on ipilimumab plus nivolumab are well equipped to manage this regimen.

Clinician Group Input

CADTH received one clinician group submission from the Ontario Health (Cancer Care Ontario) Skin Cancer Drug Advisory Committee (OH-CCO's Drug Advisory Committees). Of note, at the time OH CCO input, the proposed Health Canada indication was not line specific (i.e., indicated for the treatment of adult and pediatric patients (12 years and older and weighing at least 40 kg) with unresectable or metastatic melanoma), however, after the input was received, the indication was approved to first line (i.e., for the treatment of adult and pediatric patients 12 years of age or older with unresectable or metastatic melanoma who have not received prior systemic therapy for unresectable or metastatic melanoma). In the first line metastatic or unresectable setting, the current treatments can include single agent nivolumab, or pembrolizumab, ipilimumab plus nivolumab combination (IPI+NIVO) and BRAF targeted agents (for patients with BRAF mutations). The BRAF targeted therapy options are dabrafenib-trametinib, cobimetinib-vemurafinib, and binimetinib-encorafenib. If patients received pembrolizumab or nivolumab in first line, the subsequent line options are ipilimumab alone, or BRAF targeted therapy (for patients with BRAF mutation). If ipilimumab plus nivolumab followed by nivolumab maintenance is used in first line, only patients with a BRAF mutation have a second line option to use BRAF targeted therapy. Patients who received first line BRAF targeted therapy may be eligible for pembrolizumab, nivolumab, or ipilimumab plus nivolumab in the second line setting. If treated with pembrolizumab or nivolumab, the patient may be eligible to use ipilimumab further downstream.

According to OH-CCO's Drug Advisory Committees, the drug under review has a higher response rate than single agent nivolumab in patients with unresectable or metastatic melanoma as per the RELATIVITY 047 trial. Although there is no head-to-head comparison trial, this combination also has less toxicity than ipilimumab plus nivolumab whose treatment related adverse events are reported in CHECKMATE 067 trial, which might fill some of the unmet needs of the standard treatment.

OH-CCO's Drug Advisory Committees reported that following algorithm should be:

FIRST LINE METASTATIC / UNRESECTABLE

Patients who are not able to tolerate ipilimumab-nivolumab or who would be treated with single agent PD-1 inhibitor would be suitable for receiving drug under review in the first line metastatic or unresectable setting.

OH-CCO's Drug Advisory Committees believed that a clinically meaningful response would be improved survival, reduction in the frequency/severity of symptoms, attainment of major motor milestones, ability to perform activities of daily living, improvement of symptoms, and stabilization (no deterioration) of symptoms. Treatment response will be routinely assessed clinically, and by CT and/or PET approximately every 3 months.

OH-CCO's Drug Advisory Committees mentioned that the most likely reason to discontinue treatment would be confirmed disease progression and/or unmanageable toxicities.

OH-CCO's Drug Advisory Committees noted that the drug under review should be administered in an outpatient cancer clinic, prescribed by a medical oncologist.

Drug Program Input

The drug programs provide input on each drug being reviewed through CADTH's Reimbursement Review processes by identifying issues that may impact their ability to implement a recommendation. The implementation questions and corresponding responses from the clinical experts consulted by CADTH are summarized in Table 2.

Table 2: Summary of Drug Plan Input and pERC Response

Drug program implementation questions	pERC Response
Relevant comparators	
a) Issues with the choice of comparator in the submitted trial(s) The comparator in RELATIVITY-047 was single agent nivolumab, which is publicly funded in Canada. Nivolumab + relatlimab is proposed as an alternative to currently available PD-1 inhibitors for unresectable or metastatic melanoma. Pembrolizumab and nivolumab are both publicly funded.	Comment from the drug programs to inform pERC deliberations
b) Other implementation issues regarding relevant comparators (e.g., access/funding, covered population) Other therapies funded in Canada are potential comparators in unresectable or metastatic melanoma. These were not included as comparators in RELATIVITY-047: - Ipilimumab + nivolumab - Pembrolizumab - Dabrafenib + trametinib - Cobimetinib + vemurafenib - Binimetinib + encorafenib	Comment from the drug programs to inform pERC deliberations
Considerations for initiation of therapy	
a) Disease diagnosis, scoring or staging for eligibility RELATIVITY-047 required PD-L1 and LAG3 testing in all patients. Patients with expression or no expression were included. The study found that response was not predicted by expression of these markers.	
Should PD-L1 and LAG3 testing be done routinely in this population?	pERC noted that the results from RELATIVITY-047 did not show any difference in the subgroups response for PD-L1 and LAG3. The PFS benefit observe was irrespective of PD-L1 and LAG3 status. As a result, pERC agreed with the clinical experts that there is no need in practice for routine PD-L1 and LAG3 testing to select patients for this therapy.
What is the current status of access to LAG3 testing in jurisdictions across Canada?	pERC acknowledged the clinical experts' response that LAG3 testing is not routinely done in jurisdictions across Canada.
What is the turnaround time for testing?	pERC noted the input received from the clinical experts which stated that most tests take two weeks, and however, turnaround time for testing depends on if it is next-generation sequencing or immunohistochemistry.
Is LAG3 testing standardized?	pERC acknowledged the clinical experts' input which recognized that LAG3 testing is not routinely done.
b) Other patient characteristics for eligibility (e.g., age restrictions, comorbidities)	

Drug program implementation questions	pERC Response
The trial was in patients 12 years and older and over 40 kg. ***Should patients under 12 years/40 kg be considered?***	Patients under 12 years of age or who weigh less than 40 kg would not be considered. pERC noted that the Health Canada indication does not include children under 12 years of age. The safety and efficacy of nivolumab and relatlimab FDC have not been established in pediatric patients under the age of 12 years or in patients 12 years of age or older and weighing less than 40 kg; this is outlined in the Health Canada product monograph.
Patients with active, known, or suspected autoimmune disease were excluded (exceptions: T1 diabetes mellitus, hypothyroidism on hormone replacement, skin disorders). ***Should patients with autoimmune disorders be considered at the discretion of the treating physician?***	pERC agreed with the clinical experts that patients with autoimmune disorders would be considered provided that their disease is not active. Hence, patients with active autoimmune disorders would not be eligible for reimbursement.
c) Prior therapies required for eligibility There are no other LAG3 inhibitors currently available in Canada. ***Should the enrollment criteria regarding prior neoadjuvant/adjuvant treatment used in RELATIVITY-047 be used?***	pERC recognized that nivolumab and relatlimab would be an alternative therapy in patients who progress on BRAF/MEK therapies used in the adjuvant setting. While pERC noted that the enrollment criteria permitted neoadjuvant or adjuvant IFN therapy with the last dose at least 6 weeks prior to randomization, pERC noted the infrequent and rare use of IFN therapy in neoadjuvant or adjuvant in Canada. Prior adjuvant or neoadjuvant anti-PD-1 or anti-CTLA-4 therapy should be followed as per RELATIVITY-047.
Should patients with potentially resectable disease be eligible? Patients enrolled had previously untreated unresectable or metastatic melanoma. Currently, per CADTH's provisional funding algorithm, single agent PD1 inhibitors are funded in first-line or second-line after BRAF targeted therapy. ***Are there data to support the use of nivolumab + relatlimab in the second line after BRAF targeted therapy?***	pERC concluded that patients who are not currently resectable would be eligible. pERC noted that this question is out of scope for this review as the nivolumab and relatlimab is indicated for first line use only.
d) Eligibility to re-treatment ***Should re-initiation of treatment be permitted for those who chose to take a treatment break but did not experience progression or unacceptable toxicity while on treatment?***	pERC agreed with the clinical experts that re-initiation of treatment would be permitted for those who chose to take a treatment break but did not experience progression or unacceptable toxicity while on treatment on a case-by-case basis based on the discretion of the treating clinician.

Drug program implementation questions	pERC Response
Should re-initiation be considered in the case of progression while off therapy? After a defined treatment break duration?	pERC agreed with the clinical experts that re-initiation would be considered in the case of progression while off therapy, and acknowledged that commonly, progression after a 6-month break is accepted as a guideline to reinstitute treatment.
e) Special subtypes (not explicitly mentioned in the indication) to consider separately for eligibility ***Patients with active CNS disease were excluded. Should they be eligible?*** ***Patients with uveal melanoma were excluded. Should they be eligible?***	pERC considered the input from the clinical experts and concluded that patients with active CNS and patients with uveal melanoma would not be eligible for nivolumab and relatlimab.
Considerations for discontinuation of therapy	
a) Definition of loss of response, absence of clinical benefit, or disease progression In RELATIVITY-047, treatment was continued until progression or unacceptable toxicity. ***What is the most appropriate definition for progression?*** Patients could also continue treatment beyond progression if demonstrating a clinical benefit– ***Is this appropriate in any scenario other than pseudoprogression?***	[redacted] According to the clinical experts, progression is based on the RECIST criteria- immunotherapy subset RECIST 1.1 criteria. The clinical experts also acknowledged that there is some pseudoprogression with immunotherapy. [redacted]pERC considered the input from the clinical experts and concluded that progression should be left up to the treating physician to determine. pERC does not recommend continuing the therapy in those with confirmed progression.
b) Treatment interruptions ***If treatment is interrupted, can it be resumed? Is there a specific timeframe?*** ***Can treatment be resumed after holding for a toxicity that resolves to acceptable levels?***	pERC agreed with the clinical experts that if treatment is interrupted, it can be resumed. The timeframe is after toxicity is resolved, as long as, it was not a life-threatening toxicity. Yes, treatment can be resumed after holding for a toxicity that resolves to acceptable levels.
Considerations for prescribing of therapy	
a) Dosing, schedule/frequency, dose intensity The fixed dose combination of 160 mg of relatlimab and 480 mg of nivolumab is given every 4 weeks. ***Is there potential for any other dosing options? Weight-based?***	Nivolumab plus relatlimab FDC was manufactured as fixed dose, according to the clinical experts, weight based adjusted remuneration should not be based on weight dosing.
Generalizability	
a) Populations of interest matching the indication but with insufficient data	

Drug program implementation questions	pERC Response
Patients with ECOG > 1 were excluded from the trial. ***Should they be eligible for treatment?***	pERC concluded that patients with good performance status should be eligible for treatment and the decision to treat a patient with PS 2 or higher should be up to the treating physician.
b) Populations outside the indication or reimbursement request but of interest to jurisdictions ***Should any patients considered appropriate for treatment with combination ipilimumab + nivolumab be considered for nivolumab + relatlimab?*** ***Is there any evidence or clinical rationale to choose nivolumab + relatlimab over ipilimumab + nivolumab?***	pERC noted the input from the clinical experts which stated if nivolumab and relatlimab is approved for reimbursement, then both options (nivolumab and ipilimumab, and nivolumab and relatlimab) could be considered for patients. pERC discussed that there is no direct evidence comparing nivolumab and relatlimab to nivolumab and ipilimumab, and while the indirect treatment comparisons submitted by the sponsor included this comparison the evidence from this indirect comparison is interpreted with caution.
a) Patients on active treatment with a time-limited opportunity to switch to the drug(s) under review ***Should patients currently receiving first-line treatment for unresectable or metastatic melanoma with no disease progression be eligible to switch to nivolumab + relatlimab?*** ***Should patients who experience toxicity with ipilimumab and discontinue ipilimumab without progression be able to switch to nivolumab + relatlimab?*** ***Should patients being treated with second-line pembrolizumab or nivolumab (when BRAF targeted therapy was used in the first-line) be eligible to switch to nivolumab + relatlimab?***	pERC agreed with the clinical experts that patients currently receiving first-line treatment for unresectable or metastatic melanoma with no disease progression would not be eligible to switch to nivolumab and relatlimab. pERC agreed with the clinical experts that patients who experience toxicity with ipilimumab and discontinue ipilimumab without progression would continue with nivolumab alone and would not be able to switch to nivolumab and relatlimab. pERC noted that this question is out of scope as the Health Canada indication is specific to first line therapy as well as the evidence reviewed.
Funding algorithm (oncology only)	
Drug may change place in therapy of comparator drugs	Comment from the drug programs to inform pERC deliberations
Drug may change place in therapy of drugs reimbursed in previous lines	Comment from the drug programs to inform pERC deliberations
Drug may change place in therapy of drugs reimbursed in subsequent lines ***Will patients be eligible for single agent ipilimumab after progression?*** ***Will patients be eligible for any other ICI therapy after progression?***	pERC noted that these questions are out of scope for the current CADTH review which is focused on nivolumab and relatlimab in one particular line of therapy. Notwithstanding this, pERC recognized the value of ipilimumab monotherapy in the second line setting. pERC noted that provinces could address this with an updated funding algorithm.

Drug program implementation questions	pERC Response
Will patients with BRAF mutation be eligible for BRAF targeted therapy after progression?	
Complex therapeutic space with multiple lines of therapy, subpopulations, or competing products	Comment from the drug programs to inform pERC deliberations
Other aspects:	Comment from the drug programs to inform pERC deliberations
Care provision issues	
a) Companion diagnostics (e.g., access issues, timing of testing) ***Will LAG3 testing be necessary?***	pERC agreed with the clinical experts that LAG3 testing is not necessary.
b) Other care provision issues ***In the event of toxicity to nivolumab + relatlimab, would switching to single agent nivolumab be reasonable/permitted?***	pERC agreed with the clinical experts that if toxicity is deemed to be related to relatlimab by the clinician, then it would be reasonable for the patient to switch to single agent nivolumab.
System and economic issues	
a) Additional costs to be considered (other than related to care provision as detailed above) ***Possible need for and cost of implementing LAG3 testing in practice.***	Comment from the drug programs to inform pERC deliberations
b) Presence of confidential negotiated prices for comparators ***Confidential prices for other first-line therapies (ICI and BRAF targeted therapies)***	Comment from the drug programs to inform pERC deliberations

BRAF = B-Raf proto-oncogene; ECOG = Eastern Cooperative Oncology Group; ICI = Immune checkpoint inhibitor; IHC= immunohistochemistry; LAG3 = lymphocyte activation gene 3; NGS = next-generation sequencing; PD-L1 = programmed death-ligand 1.

Clinical Evidence

Systematic Review

Description of Studies

One pivotal, phase 2/3, double blinded, randomized controlled and ongoing trial (the RELATIVITY-047, N=714) is included in the systematic review. The objective of RELATIVITY-047 was to evaluate the comparative efficacy and safety of nivolumab plus relatlimab FDC) versus nivolumab monotherapy administered as a first-line therapy in the treatment of adult and pediatric patients 12 years of age or older with previously untreated, unresectable, or metastatic melanoma. However, no adolescents aged ≥12 to <18 years) were enrolled. A total of 714 patients were randomized 1:1 to receive nivolumab plus relatlimab FDC (n=355) or nivolumab monotherapy (n=359). The median age (range) was 63 (20-94) years old. The majority (N = 655, 91.7%) patients were metastatic stage IV at study entry. The medium duration from diagnosis to the study treatment was 1.26 years. A total of 62 (8.7%) patients received previous adjuvant or neoadjuvant treatment. A total of 275 (38.5%) patients were BRAF positive. A total of 16 (2.2%) patients from Canada and 63 (8.8%) patients from United States were included. The primary outcome was PFS. The two secondary outcomes were OS and ORR. Tertiary/exploratory outcomes included DOR, TTR and HRQOL measurements (i.e., FACT-M, EQ-5D-3L). The sample size for the study was based on a primary endpoint of PFS using BICR for both Phase 2 and Phase 3 study. Results presented in this submission reflect the phase 3 component of RELATIVITY-047. The final analysis for PFS was conducted after a median follow-up of 13.2 months. The final analysis for OS and ORR was conducted after a median follow-up of 19.3 months. Results for median DOR and TTR are based on the updated descriptive analysis conducted after a median follow-up of 25.3 months. HRQOL measurements (i.e., FACT-M, EQ-5D-3L) were conducted after a median follow-up of 19.3 months. The objective of the safety outcomes was to assess the overall safety and tolerability of nivolumab plus relatlimab and nivolumab. Safety data reported in this review was based after a median follow-up of 25.3 months.

Efficacy Results

Based on the final analysis after a median follow up of 13.2 months, the median PFS was 10.12 months (95%ci: 6.37 to 15.74) in the nivolumab plus relatlimab FDC group, which was statistically significantly and clinically meaningful longer compared to 4.63 months in the nivolumab monotherapy group (HR: NIVO+ RELA FDC vs. NIVO: 0.75, 95% CI 0.62 to 0.92; p=0.0055). The observed PFS benefit of nivolumab plus relatlimab FDC compared with nivolumab monotherapy were showed in an updated descriptive analysis after a median follow up of 25.3 months. Subgroup and sensitivity analyses of PFS were largely consistent with the primary analysis.

After a median follow-up of 19.3 months, the median OS was not reached in the nivolumab plus relatlimab group compared to 34.10 months in the nivolumab group. The between group difference (NIVO+RELA FDC vs. NIVO) for median OS did not reach statistical significance at the OS final analysis after a median follow up of 19.3 months (HR 0.80 [95% CI 0.64 to 1.01]; p=0.0593). Similarly, after a median follow up of 25.3 months, median OS was not reached in the nivolumab plus relatlimab group compared to 33.18 month in the nivolumab group in updated descriptive analysis. Therefore, the comparative OS of nivolumab plus relatlimab FDC compared with nivolumab monotherapy was uncertain.

Based on descriptive final analyses, a total of 10.3% (95% CI: 3.4 % to 17.3%) more patients in the nivolumab plus relatlimab FDC group achieved an objective response compared with the nivolumab group after a median follow up of 19.3 months. Consistent ORR benefit was also observed in the updated descriptive analysis after a median follow-up of 25.3 months. A total of 9.8% (95% CI: 2.8 % to 16.8%) more patients in the nivolumab plus relatlimab FDC group achieved an objective response compared with the nivolumab group.

In terms of complete response (CR) and progressive disease (PD), no formal statistically analysis or any descriptive analysis was done to report the between group difference, 95% CI of between group difference. No HR (95%CI) was provided. Therefore, the comparative CR and PD of nivolumab plus relatlimab FDC compared with nivolumab monotherapy remains inconclusive.

After a median follow-up of 25.3 months, no statistical and clinical meaningful between group difference were observed for DOR. TTR appeared the same after a median follow-up of 25.3 months. However, no between group difference, no HR was reported for TTR. The comparative DOC and TTR of nivolumab plus relatlimab FDC compared with nivolumab monotherapy remains uncertain.

After a median follow-up of 19.3 months, HRQoL (FACT-M, EQ-5D-3L utility index scores and EQ-5D-VAS) in the nivolumab plus relatlimab FDC and nivolumab groups remained generally stable (no clinical meaningful improvement or deterioration) during the treatment period. There were little to no differences between nivolumab plus relatlimab FDC and nivolumab monotherapy in FACT-M, EQ-5D-3L utility index scores, and EQ-5D-VAS.

It should be noted that no adolescents (aged ≥12 to 18 years) were enrolled in the pivotal study. However, in the Health Canada product monograph[40], the indication of nivolumab plus relatlimab FDC includes for the use of pediatric patients 12 years of age or older and weighing at least 40 kg. In the product monograph, it was indicated that use of nivolumab plus relatlimab FDC in pediatric patients is supported by predicted drug exposures at the recommended nivolumab plus relatlimab FDC dose that are expected to result in similar safety and efficacy to that of adults. The safety and efficacy of NIVOLUMAB PLUS RELATLIMAB FDC have not been established in pediatric patients under the age of 12 years or in patients 12 years of age or older and weighing less than 40 kg.[40]

Harms

The proportion of patient with at least one treatment emergent adverse events appeared similar in the nivolumab plus relatlimab FDC group compared with the nivolumab monotherapy group (99.2% in the nivolumab plus relatlimab FDC group vs. 95.8% in the NIVO monotherapy group). However, the most common any grade AEs (occurred in >20% patients in either of the two groups) appeared to occur in more patients in the nivolumab plus relatlimab FDC group than the nivolumab monotherapy group, such as fatigue (NIVO+RELA FDC vs. NIVO: 30.7% vs. 20.9%) and diarrhea (27.9% vs. 19.5%). The frequency of SAEs appeared similar in both groups and the individual SAE events were relatively rare. With the exception of malignant neoplasm progression (NIVO+RELA FDC vs. NIVO: 3.9% vs. 5.6%), there were no other SAEs in more than 2% of patients in either group. The frequency of withdrawal due to adverse events also appeared numerically higher in the nivolumab plus relatlimab FDC group than in the nivolumab monotherapy group (NIVO+RELA FDC vs. NIVO: 23.1% vs. 15.9%). Discontinuation treatment due to specific AEs occurred in less than 2% patients in either of the groups with the exception of malignant neoplasm progression (NIVO+RELA FDC vs. NIVO: 1.7% vs. 2.8%). The frequency of death due to AEs (i.e., study drug toxicity) was rare in both groups (NIVO+RELA FDC vs. NIVO: 1.1% vs. 0.6%). Adrenal insufficiency was considered as particular special immune-mediated adverse event (IMAE), which occurred numerically higher in the nivolumab plus relatlimab FDC group than in the nivolumab group (5.6% vs.1.1%). The other particular notable harm, myocarditis, rarely occurred (1.7% vs. 0.6%). It was also noted that Grade 3/4 all-causality adverse events were numerically more frequent with nivolumab plus relatlimab FDC versus nivolumab (NIVO+RELA FDC vs. NIVO: 44.8% vs. 36.8%). Overall, the safety profile of nivolumab plus relatlimab FDC was considered manageable and consistent with the known mechanisms of action of relatlimab or nivolumab. No new safety signal was identified.

Critical Appraisal

Appropriate methods of randomization, blinding and allocation concealment were reported. Objective outcomes and validated health related outcomes were assessed. However, minimal important between group difference, which is the threshold used for the GRADE for all outcomes, are not available. Therefore, clinical expert opinion informed the thresholds to determine whether the between group difference observed for each outcome are clinically meaningful or not.

Metastatic stage M1c was relatively higher in the nivolumab plus relatlimab FDC group (n=151, [42.5%]) than in the nivolumab monotherapy group (n=127, [35.4%]), however, the clinical experts consulted for this review stated that minor between group imbalances of metastatic stage M1c would have been unlikely to impact the comparative study results between the nivolumab plus relatlimab FDC and nivolumab monotherapy groups.

In terms of the OS assessment, OS was designed and assessed as a secondary outcome, the study was not powered to assess OS between group difference at the prespecified final analysis (after a median follow up of 19. 3 months) and updated analysis (after a follow up of 25.3 months). Therefore, the comparative efficacy on OS of nivolumab plus relatlimab FDC compared with nivolumab remains uncertain.

The statistical significance of ORR (per BICR) could not be formally tested due to its position in the statistical hierarchy because the OS final analysis did not reach statistical significance. As a result, ORR, as well as complete response (CR) and progression disease (PD) (which were part of the overall response analysis), are based on only descriptive analyses after a median follow-up of 19.3

months. Only descriptive analyses without between group difference or hazard ratio (HR) were reported. Therefore, results on ORR, CR and PD should be interpreted with caution.

DOR and TTR were assessed as tertiary or exploratory outcomes but was not controlled for the hierarchical testing procedure to control type 1 error. Analyses of duration of response (DOR) and time to response (TTR) were not statistically powered and were reported using descriptive statistics only. No between group difference were reported for DOR or TTR, although HR was reported for DOR; overall, the findings of DOR and TTR should be viewed as supportive evidence only.

Similarly, FACT-M and EQ-5D-3L were assessed as tertiary/exploratory outcomes but was not controlled for the hierarchical testing procedure to control type 1 error. For these patients reported HRQOL outcomes (FACT-M and EQ-5D-3L), there may have been differential recall bias. Overall, the magnitude and direction of the impact of the recall bias on the patient reported HRQoL outcomes is unknown. HRQoL analyses were not statistically powered and were reported using descriptive statistics.[42] and overall, the findings of HRQOL should be viewed as supportive evidence only.

All subgroup analysis were not part of the randomization scheme, imbalances in characteristics may bias the results observed between the subgroups. In addition, the subgroup analysis may not be powered to detect the between group difference in each subgroup. Therefore, the findings of the subgroup analysis should be viewed as supportive evidence only.

In addition, one of the limitations of the RELATIVITY-047 trial is lack of comparison to current standard of care of therapy, except nivolumab monotherapy, the comparative efficacy and safety of nivolumab plus relatlimab FDC compared with Ipilimumab + nivolumab, encorafenib + binimetinib, dabrafenib +trametinib, vemurafenib+ combimetinib, ipilimumab, pembrolizumab, dabrafenib and trametinib is unknown.

It is uncertain whether the finding can be generalized to patients with CNS metastases or patients with ECOG PS > 1 as no such patients were included in the study. Only 17 (2.4%) patients with brain metastasis were included (1.7% and 3.1% in the nivolumab plus relatlimab FDC group and nivolumab monotherapy group respectively). Patients with active CNS metastases were excluded. The clinical experts CADTH consulted for this review indicated that while higher ECOG performance status (>1) usually indicates more severe disease and more likely with unfavorable prognosis, that the nivolumab plus relatlimab FDC combination treatments could be extended to patients with ECOG >1. In terms of patients with CNS metastasis, the clinical experts CADTH consulted for this review indicated that additional studies are needed to understand the comparative efficacy and safety of nivolumab plus relatlimab FDC versus nivolumab monotherapy in patient with CNS metastasis.

Finally, it should be noted that although age ≥12 years was an inclusion criterion, no children (≥ 12 to < 18 years old) were enrolled in the pivotal study. Therefore, the comparative efficacy and safety profile of nivolumab plus relatlimab FDC versus nivolumab monotherapy is unknown whether the findings from the RELATIVITY-047 trial can be generalized to adolescent patients (≥ 12 to < 18 years old) remains unknown. However, in the Health Canada product monograph, it is indicated that the use of nivolumab plus relatlimab FDC in pediatric patients 12 years of age or older and weighing at least 40 kg is supported by predicted drug exposures at the recommended nivolumab plus relatlimab FDC dose that are expected to result in similar safety and efficacy to that of adults. One clinical expert CADTH consulted for this review indicated that pediatric patients with unresectable or metastatic melanoma should be enrolled in clinical trials, if available, to assess the efficacy and safety profile of the nivolumab plus relatlimab FDC treatment. The other clinical expert CADTH consulted for this review indicated that because of the potential unfeasibility of the trials on the pediatric patients, use of nivolumab plus relatlimab FDC in adolescents should be considered on a case-by-case basis - especially if body habitus is like an adult or close to an adult. The clinical expert noted that currently IO is given in the pediatric population, and it is well tolerated.

GRADE Summary of Findings and Certainty of the Evidence

Methods for Assessing the Certainty of the Evidence

For pivotal studies and RCTs identified in the sponsor's systematic review, GRADE was used to assess the certainty of the evidence for outcomes considered most relevant to inform CADTH's expert committee deliberations, and a final certainty rating was determined as outlined by the GRADE Working Group. Following the GRADE approach, evidence from RCTs started as high-

certainty evidence and could be rated down for concerns related to study limitations (which refers to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias.

The selection of outcomes for GRADE assessment was based on the sponsor's Summary of Clinical Evidence, consultation with clinical experts, and input received from patient and clinician groups and public drug plans. The following list of outcomes was finalized in consultation with expert committee members: PFS, OS, ORR, DOR, HRQOL (i.e., FACT-M, EQ-5D-3L utility index and EQ-5D- VAS) change from cycle baseline after a median follow-up of 19.3 months and at a fixed landmark timepoint of 24 months, as well as notable harms (i.e., myocarditis and adrenal insufficiency).

When possible, certainty was rated in the context of the presence of an important (nontrivial) treatment effect; if this was not possible, certainty was rated in the context of the presence of any treatment effect (i.e., the clinical importance is unclear). In all cases, the target of the certainty of evidence assessment was based on the point estimate and where it was located relative to the threshold for a clinically important effect (when a threshold was available) or to the null. For this review, the target of the certainty of evidence assessment was based on the presence of absence of a clinically important effect, as informed by MIDs and thresholds suggested by the clinical experts (for all outcomes). Results of GRADE Assessments

Table 3: Summary of Findings for nivolumab plus relatlimab FDC Versus nivolumab monotherapy for the treatment of adult and pediatric patients (12 years and older and weighing at least 40 kg) with unresectable or metastatic melanoma who have not received prior systemic therapy for unresectable or metastatic melanoma

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			NIVO	NIVO+RELA	Difference		
PFS							
PFS per BICR using RECIST v1.1 Median follow-up: 13.2 months	714 (1 RCT)	PFS events (i.e., disease progression or death) at data cut-off: • Nivolumab plus relatlimab: 507 per 1,000 • Nivo: 588 per 1,000 • HR = 0.75 (95% CI: 0.62 to 0.92) Median (95% CI) PFS at data cut-off, months: • Nivolumab plus relatlimab: 10.12 (6.37 to 15.74) • Nivo: 4.63 (3.38 to 5.62)				High[a]	Nivolumab+relatlimab results in a clinically important increase in PFS when compared with Nivolumab monotherapy.
OS							
OS per DMC Median follow-up: 19.3 months	714 (1 RCT)	OS events (i.e., deaths) at data cut-off: • Nivolumab plus relatlimab: 386 per 1,000 • Nivo: 446 per 1,000 • HR = 0.80 (0.64 to 1.01) Median (95% CI) OS at data cut-off, months: • Nivolumab plus relatlimab: NA (34.20 to NA) • Nivo: 34.10 (25.23 to NA)				Low[b]	Nivolumab+relatlimab may result in a clinically important increase in OS when compared with Nivolumab monotherapy.
ORR							
ORR (CR + PR) per BICR using RECIST v1.1 Median follow up: 19.3 months	714 (1 RCT)	OR (95% CI): 1.58 (1.16 to 2.15)	326 per 1,000	431 per 1,000 (379 to 484 per 1,000)	103 more per 1,000 (34 to 173 more per 1,000)	Moderate[c]	Nivolumab+relatlimab likely results in a clinically important increase in ORR when compared with Nivolumab monotherapy.
DOR							
DOR per BICR using RECIST v1.1	276 (1 RCT)	DOR events (i.e., progression or death, following first response) at data cut-off:				Low[d]	Nivolumab+relatlimab may result in little to no

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			NIVO	NIVO+RELA	Difference		
Median follow up: 25.3 months		• Nivolumab plus relatlimab: 335 per 1,000 • Nivo: 314 per 1,000 • HR = 1.07 (0.71 to 1.63) Median (95% CI) DOR at data cut-off • Nivolumab plus relatlimab: NA (39.36 to NA) • Nivo: NA (39.82 to NA)					difference in DOR when compared with Nivolumab monotherapy.
HRQOL (a median follow up of 19.3 months and the fixed landmark timepoints: 24 months)							
FACT-M							
FACT-M total score Mean change from baseline (0 = worst HRQoL; 204 = best HRQoL) Median follow up: 19.3 months	151 (1 RCT)	NR	3.563	1.756 (-1.763 to 5.275)	-1.807 (-6.561 to 2.947)	Low[e]	Nivolumab+relatlimab may result in little to no difference in HRQoL as measured by the FACT-M when compared with Nivolumab monotherapy.
EQ-5D-3L utility index							
EQ-5D-3L utility score Mean change from baseline (0 = as bad as dead; 1 = perfect health) Median follow-up: 19.3 months	150 (1 RCT)	NR	0.002	0.009 (-0.036 to 0.053)	0.007 (-0.052 to 0.066)	Low[e]	Nivolumab+relatlimab may result in little to no difference in HRQoL as measured by EQ-5D-3L utility values when compared with Nivolumab monotherapy.
EQ-5D-3L VAS							
EQ-5D-3L VAS Mean change from baseline (0 = worst health imaginable; 100 = best health imaginable) Median follow up: 19.3 months	150 (1 RCT)	NR	2.084	2.840 (-0.454 to 6.135)	0.757 (-3.651 to 5.164)	Low[e]	Nivolumab+relatlimab may result in little to no difference in HRQoL as measured by the EQ-5D-3L VAS when compared with Nivolumab monotherapy.
Notable harms (i.e., AEs of special interest)							
Myocarditis Median follow-up: 25.3 months	714 (1 RCT)	NR	6 per 1,000	17 per 1,000 (NR)	NR	Low[f]	Nivolumab+relatlimab may result in an increase in the proportion of patients who experience myocarditis when compared with Nivolumab monotherapy. The clinical importance of the increase is uncertain.
Adrenal Insufficiency	714 (1 RCT)	NR	11 per 1,000	56 per 1,000 (NR)	NR	Low[f]	Nivolumab+relatlimab may result in an increase in the proportion of patients who experience adrenal

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			NIVO	NIVO+RELA	Difference		
Median follow-up: 25.3 months							insufficiency when compared with Nivolumab monotherapy. The clinical importance of the increase is uncertain.

AE = adverse event; CI = confidence interval; ; DOR = duration of response; FACT-M = Functional Assessment of Cancer Therapy – Melanoma; HRQoL = health-related quality of life; NA = not available (or not reached); Nivo = nivolumab; NIVO+RELA = nivolumab+relatlimab FDC; NR = not reported; ORR = overall response rate; OS = overall survival; PFS = progression free survival; RCT = randomized controlled trial; RECIST = Response Evaluation Criteria in Solid Tumours; Rela = relatlimab; VAS = visual analog scale

Note: The analysis of ORR, DOR and HRQOL (-FACT-M total score and EQ-5D-3L) were not adjusted for multiple comparisons.

[a] In the absence of available data for the between-group difference in event probabilities at clinically relevant time points, the judgment of imprecision was based on the 95% CI for the HR using the null as the threshold. The clinical importance of the between-group difference was judged based on the input of the clinical experts consulted by CADTH for the review.

[b] Rated down 1 level for serious imprecision. In the absence of available data for the between-group difference in event probabilities at clinically relevant time points, the judgment of imprecision was based on the 95% CI for the HR using the null as the threshold. The 95% CI for the HR included the possibility of little to no difference (i.e., included the null). The clinical importance of the between-group difference was judged based on the input of the clinical experts consulted by CADTH for the review. Rated down 1 level for serious indirectness. The follow-up time was not sufficient for assessing OS in this population.

[c] Rated down 1 level for serious imprecision. Based on the threshold for a clinically important between-group difference suggested by the clinical experts of 50 to 100 events per 1,000 patients, the point estimate suggests a benefit; however, the lower bound of the 95% CI suggests little to no difference.

[d] Rated down 2 levels for very serious imprecision. In the absence of available data for the between-group difference in event probabilities at clinically relevant time points, the judgment of imprecision was based on the 95% CI for the HR using the null as the threshold. The 95% CI for the HR included the possibility of both benefit and harm for nivolumab plus relatlimab compared with nivolumab monotherapy.

[e] Rated down 2 levels for very serious risk of bias due to missing outcome data. Data were available for 21% of randomized patients. In the absence of a known threshold for a clinically important between-group difference, the null was used as the threshold.

[f] Rated down 2 levels for very serious imprecision. The results are based on very few events in each group (6/355 versus 2/359 for myocarditis and 20/355 versus 4/359 for adrenal insufficiency in the nivolumab + relatlimab and nivolumab groups, respectively).

Long-Term Extension Studies

Not available

Indirect Comparisons

Description of Studies

Overall, two ITC reports were submitted. One ITC, a Bayesian network meta-analysis (NMA), assessed the safety and efficacy of relatlimab + nivolumab relative to other IO agents for adult patients in the first-line management of patients with advanced melanoma. The second ITC (ITC2), a patient-level propensity-weighted comparison, assessed relatlimab + nivolumab relative to ipilimumab + nivolumab among patients with advanced melanoma treated first-line.

Efficacy Results

The first ITC, a Bayesian NMA assessed relatlimab + nivolumab relative to nivolumab monotherapy, ipilimumab monotherapy, nivolumab (1mg/kg) + ipilimumab (3mg/kg), nivolumab (3mg/kg) + ipilimumab (1mg/kg), pembrolizumab and cobimetinib + atezolizumab.

ITC1 indicated that relatlimab + nivolumab is associated with improvements to OS relative to ipilimumab monotherapy at 48 months (HR:0.48, 95% CrI: 0.34, 0.69). For PFS at 48 months, relatlimab + nivolumab is associated with improvements relative to ipilimumab (HR: 0.32, 95% CrI: 0.22, 0.48), pembrolizumab (HR: 0.59, 95% CrI: 0.35, 0.97), and [redacted]

For ITC2, the results indicated that there was no difference between relatlimab + nivolumab relative to ipilimumab (3mg/kg) + nivolumab (1mg/kg) with respect to PFS and OS.

No data were available in either ITC with respect to ORR, TTP, or any patient-reported outcome.

Harms Results

In ITC1, relatlimab + nivolumab was associated with higher proportions of patients having grade 3-4 treatment-related adverse events when compared to nivolumab (OR: 2.08, 95% CrI:1.39, 3.14), [redacted] and pembrolizumab (OR: 1.99, 95% CrI: 1.01, 3.87), and was associated with lower proportions of patients experiencing these events relative to nivolumab (1mg/kg) + ipilimumab (3mg/kg) (OR: 0.43, 95% CrI: 0.25, 0.73). For discontinuations due to adverse events, [redacted]

No comparative data were presented from ITC2 with respect to safety outcomes, as no formal statistical comparison of the differences in safety events were conducted.

Critical Appraisal

Sponsor-submitted evidence from ITC1 was provided with comparisons to non-IO interventions of interest, such as BRAF/MEK inhibitors, but owing to several challenges associated with mixed mutation status and the evidence from treatment nodes connecting to this network of evidence, no clear conclusions could be drawn with respect to comparative efficacy and safety within this population. Several trials reporting on OS for the IO network of evidence still had ongoing observation for survival data at the time of analysis, so there may be additional uncertainty with these comparisons.

Economic Evidence

Cost and Cost-Effectiveness

Component	Description
Type of economic evaluation	Cost-utility analysis Partitioned Survival Model
Target population	Adult and pediatric patients (12 years and older and weighing at least 40kg) with unresectable or metastatic melanoma
Treatment	nivolumab plus relatlimab (NIVO+RELA)
Dose Regimen	480 mg nivolumab and 160 mg relatlimab every 4 weeks until disease progression or unacceptable toxicity.
Submitted Price	Nivolumab 240 mg plus relatlimab 80 mg, in a fixed dose combination: $8,315 per 20 mL vial
Treatment Cost	$16,630 every 28-days
Comparators	nivolumab monotherapy ipilimumab monotherapy pembrolizumab monotherapy nivolumab plus ipilimumab vemurafenib plus cobimetinib dabrafenib plus trametinib encorafenib plus binimetinib
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime (25 years)
Key data sources	RELATIVITY-047 Sponsor submitted systematic review and NMA
Key limitations	The CADTH clinical review could not reach definitive conclusions regarding relative treatment efficacy for nivolumab plus relatlimab compared with relevant comparators for OS or PFS outcomes. Additionally, a stratified analysis should have been conducted given that some comparator treatments are indicated for the BRAF-positive sub-population. Issues with the sponsor's modeling approach Predicted values for the OS curve were capped by the general population mortality risk, which was inappropriate for a partitioned survival model and impedes the model's ability to properly reflect transitions between health states. The sponsor used a two-part extrapolation approach for PFS in their model, which is not recommended by CADTH submission guidelines. The use of such an approach hinders the ability of the model to reflect decision uncertainty. Use of the Gompertz distribution to predict long term survival implied that some patients would be cured as a result of treatment. Clinical experts consulted by CADTH suggested less optimistic predictions of long-term survival were required.
CADTH reanalysis results	The CADTH base case addressed some of the key identified limitations: the cap on predicted OS values was removed; predicted PFS values for and nivolumab were generated from a parametric survival model; and predicted values for OS and PFS for nivolumab plus relatlimab and nivolumab monotherapy were assumed to follow an exponential, rather than a Gompertz distribution. In the CADTH base case, three treatments were identified to be on the cost-effectiveness frontier. Nivolumab plus relatlimab was the most costly and the most effective.

Component	Description
	A price reduction for nivolumab/relatlimab is required to be considered cost-effective at a willingness to pay threshold of $50,000 per QALY gained.

Budget Impact

CADTH identified the following limitations in the sponsor's base case: uncertainty in estimates of market size resulting from assuming: i) 92.67% of patients will be diagnosed at Stage I-III (resectable); ii) [redacted] of patients will recur to Stage III (unresectable) or Stage IV following an initial diagnosis of Stage I-III (resectable); and iii) [redacted] of patients will be diagnosed at Stage III (unresectable).

CADTH performed a reanalysis, which explored how changes in each assumption affected the estimated budget impact. Clinical experts consulted by CADTH assumed: i) 85% of patients will be diagnosed at Stage I-III (resectable); ii) 5% of patients will recur to Stage III (unresectable) or Stage (IV) following an initial diagnosis of Stage I-III (resectable); and iii) 10% of patients will be diagnosed at Stage III (unresectable).

Based on the CADTH base case, the budget impact from the introduction of NIVO+RELA is expected to be $4,734,946 in Year 1, $12,890,614 in Year 2, and $16,679,027 in Year 3. The three-year net-budget impact was estimated to be $34,304,588.

pERC Information

Members of the Committee:

Dr. Maureen Trudeau (Chair), Mr. Daryl Bell, Dr. Phillip Blanchette, Dr. Kelvin Chan, Dr. Matthew Cheung, Dr. Michael Crump, Dr. Jennifer Fishman, Mr. Terry Hawrysh, Dr. Yoo-Joung Ko, Dr. Christian Kollmannsberger, 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: December 5, 2023

Regrets:

3 expert committee members did not attend.

Conflicts of interest:

None