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Re-Treatment With Immune Checkpoint Inhibitors

Rapid Review

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Abbreviations

cHL	classical Hodgkin lymphoma
CSCC	cutaneous squamous cell carcinoma
ICI	immune checkpoint inhibitor
NSCLC	non–small cell lung cancer

Key Messages

- We did not find any evidence regarding the clinical effectiveness and safety of second re-treatment with pembrolizumab for non–small cell lung cancer, classical Hodgkin lymphoma, and advanced melanoma.
- We did not find any evidence regarding the clinical effectiveness and safety of second re-treatment with cemiplimab for cutaneous squamous cell carcinoma.
- We did not find any evidence-based guidelines regarding the second re-treatment with immune checkpoint inhibitors for non–small cell lung cancer, classical Hodgkin lymphoma, advanced melanoma, and cutaneous squamous cell carcinoma.

Context and Policy Issues

What Are Immune Checkpoint Inhibitors?

Immune checkpoint inhibitors (ICIs) are a type of immunotherapy using monoclonal antibodies to treat cancer.[1] The immune system cells, such as T-cells, have protein receptors on cell surface called immune checkpoints that help keep the immune responses in check, preventing autoimmune diseases.[1] Some cancer cells evade destruction from the immune system by triggering the expression of immune checkpoints, thus stopping the immune system from attacking cancer cells.[1] By blocking these checkpoints, ICIs reactivate and boost the T-cell mediated immune response against cancer cells and destroy them.[1]

Seven ICIs have been approved by Health Canada for immune therapy of various cancer types.[1] They are grouped into 3 main types of ICIs and named after the checkpoint proteins such as anti–PD-1 (pembrolizumab, nivolumab, cemiplimab), anti–PD-L1 (atezolizumab, avelumab, durvalumab), and anti–CTLA-4 (ipilimumab).[1] This report focuses on 2 anti–PD-1 antibodies, pembrolizumab and cemiplimab.

Pembrolizumab, marketed as Keytruda, has been approved without conditions by Health Canada for the treatment of various types of cancer including advanced melanoma, non–small cell lung cancer (NSCLC), lung cancer, renal cell carcinoma, advanced colorectal cancer, endometrial carcinoma, head and neck squamous cell carcinoma, stomach cancer, breast cancer, cervical cancer, and gallbladder cancer.[2] Pembrolizumab has also been approved with conditions to treat classical Hodgkin lymphoma (cHL), mediastinal B-cell lymphoma, and urothelial carcinoma.[2]

Cemiplimab, marketed as Libtayo, has been initially approved by Health Canada to treat advanced cutaneous squamous cell carcinoma (CSCC), and now is extended to treat other cancers including NSCLC, basal cell carcinoma, and cervical cancer.[3]

What Is the Current Practice?

The recommended dose of pembrolizumab is 200 mg or 400 mg in adults, or 2 mg/kg (up to a maximum of 200 mg) in children (12 years and older), given intravenously for about 30 minutes every 3 weeks or every

6 weeks.[2] The recommended dose of cemiplimab is 350 mg every 3 weeks administered as an IV infusion over 30 minutes.[3] These ICIs can be given to patients for a fixed duration or until progression. For instance, several pivotal trials on immunotherapy of NSCLC have shown that a maximum 35 cycles or 2 years of treatment with pembrolizumab demonstrated significant survival benefits.[4] Similarly, Phase I and II clinical trials and real-world observational studies have demonstrated that cemiplimab is effective, safe, and well-tolerated in most patients with CSCC, when given up to 96 weeks.[5,6]

Despite the improvements in early-stage treatments, a large proportion of patients may show relapse while off therapy or disease progression over time even with continued treatment.[7] The incidence of disease progression after ICI treatment varies from 10% to 70%, depending on the disease.[8] Subsequent treatment options, so called re-treatment or rechallenge with the same or another ICI, seems to be a suitable treatment option for patients who have disease progression after the first course of therapy with ICIs. Recent evidence from pivotal trials has shown that re-treatment with ICIs in solid tumours exhibits encouraging efficacy and acceptable safety.[7,9] For instance, the KEYNOTE trials on NSCLC allowed an additional 1 year or 17 cycles of re-treatment with pembrolizumab after completing 35 cycles and experiencing disease progression.[10] Based on the findings from those trials, reimbursement policies have been made for an additional 1 year (17 cycles) of re-treatment with pembrolizumab in all indications.[11] Similar policies have been adopted for cemiplimab, with re-treatment funded for an additional 1 year (17 cycles) in patients who completed 2 years of cemiplimab treatment and subsequently progressed and patients who discontinued cemiplimab after less than 2 years due to complete response.[12]

Why Is It Important to Do This Review?

Patients who undergo their first re-treatment may relapse again after the authorized 1-year re-treatment. Decision-makers are wondering if those patients may benefit from a second re-treatment (i.e., a third round of therapy) with the same ICIs. Particularly, pembrolizumab has been used in patients with NSCLC, cHL, or melanoma, and cemiplimab has been used in patients with CSCC.

Objective

To support decision-making about the possibility of a second re-treatment with the same ICIs, we prepared this Rapid Review to summarize and critically appraise the available studies on the efficacy and safety of a second re-treatment with pembrolizumab for NSCLC, cHL, and advanced melanoma, and the efficacy and safety of a second re-treatment with cemiplimab for CSCC. This report also aims to review the evidence-based guideline recommendations on the second re-treatment with ICIs for NSCLC, cHL, advanced melanoma, and CSCC.

Research Questions

1. What is the clinical effectiveness and safety of a second re-treatment with pembrolizumab for NSCLC, cHL, and advanced melanoma?
2. What is the clinical effectiveness and safety of a second re-treatment with cemiplimab for CSCC?

3. What are the evidence-based guideline recommendations on the second re-treatment with ICIs for NSCLC, cHL, advanced melanoma, and CSCC?

Methods

Literature Search Methods

An information specialist conducted a literature search on key resources including MEDLINE, the Cochrane Database of Systematic Reviews, the International HTA Database, the websites of Canadian and major international health technology agencies, as well as a focused internet search. The search approach was customized to retrieve a limited set of results, balancing comprehensiveness with relevancy. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. Search concepts were developed based on the elements of the research questions and selection criteria. The main search concepts were pembrolizumab, cemiplimab, or ICIs; non–small cell lung cancer, classic Hodgkin lymphoma, melanoma, or CSCC; and re-treatment. No filters were applied to limit the retrieval by study type. An additional search for guidelines was conducted with the main search concepts non–small cell lung cancer, classic Hodgkin lymphoma, melanoma, or CSCC, and ICIs or re-treatment. Search filters were applied to limit retrieval to guidelines. The searches were completed on June 12, 2024, and limited to English-language documents.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Criteria	Description
Population	Patients previously treated with pembrolizumab (RQ1) or cemiplimab (RQ2) in the advanced or metastatic setting, who then relapsed while off therapy, were treated with a second course of the same drug, and relapsed again RQ1: Patients with NSCLC, cHL, or melanoma RQ2: Patients with CSCC RQ3: Patients with NSCLC, cHL, melanoma, CSCC
Subgroup	PD-L1 expression Prior response to ICI (complete, partial, stable disease) Prior targeted therapy for advanced disease Oncogenic driver mutation (e.g., BRAF, ALK, EGFR)
Intervention	RQ1: Pembrolizumab RQ2: Cemiplimab RQ3: Pembrolizumab or cemiplimab

Criteria	Description
Comparator	Any comparator or no comparator
Outcomes	RQ1 to 2: Clinical effectiveness: ORR, PFS, OS, HRQoL; safety RQ3: Evidence-based guidelines on use of ICI after 2 successive relapses on the same drug
Study designs	RQ1 to 2: SR, HTA, RCTs (phase II, III, IV), nonrandomized studies including single-arm trials RQ3: Evidence-based guidelines

ALK = anaplastic lymphoma kinase; BRAF = v-raf murine sarcoma viral oncogene homologue B1; cHL = classical Hodgkin lymphoma; CSCC = cutaneous squamous cell carcinoma; EGFR = epidermal growth factor receptor; HRQoL = health-related quality of life; HTA = health technology assessment; ICI = immune checkpoint inhibitor; NSCLC = non–small cell lung cancer; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; RCT = randomized controlled trial; RQ = research question; SR = systematic review.

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1.

Summary of Evidence

Quantity of Research Available

A total of 378 citations were identified in the literature search. Following screening of titles and abstracts, 372 citations were excluded and 6 potentially relevant reports from the electronic search were retrieved for full-text review. No potentially relevant publications were retrieved from the grey literature search for full-text review. None of these 6 potentially relevant articles met the inclusion criteria and they were excluded from this report for various reasons. Appendix 1 presents the PRISMA[13] flow chart of the study selection.

Summary of Findings

We did not find any evidence regarding the clinical effectiveness and safety of second re-treatment with pembrolizumab for NSCLC, cHL, and advanced melanoma, or the clinical effectiveness and safety of second re-treatment with cemiplimab for CSCC. We also did not find any evidence-based guideline recommendations on the second re-treatment with ICIs for NSCLC, cHL, advanced melanoma, and CSCC.

Limitations

No evidence was identified for a relevant population that consists of patients previously treated with pembrolizumab or cemiplimab in the advanced or metastatic setting who then relapsed while off therapy, were treated with a second course of the same drug, then relapsed again.

Conclusions and Implications for Decision- or Policy-Making

No relevant literature was identified to answer the research questions; therefore, conclusions could not be provided regarding the clinical effectiveness and safety, or recommendations on, the second re-treatment with ICIs for NSCLC, cHL, advanced melanoma, and CSCC.

Recent prospective and retrospective clinical studies mostly evaluated the efficacy and safety of ICI re-treatment with the same or another ICIs for patients with solid tumours who had disease progression or relapse after the initial treatment with ICIs.[7,9,10,14-16] We did not find any evidence about the second re-treatment with ICIs, particularly pembrolizumab or cemiplimab, if those patients relapse again. Future investigation on immunotherapy rechallenge is needed to evaluate whether a second re-treatment (i.e., a third round of therapy) with ICIs should be given for those patients.

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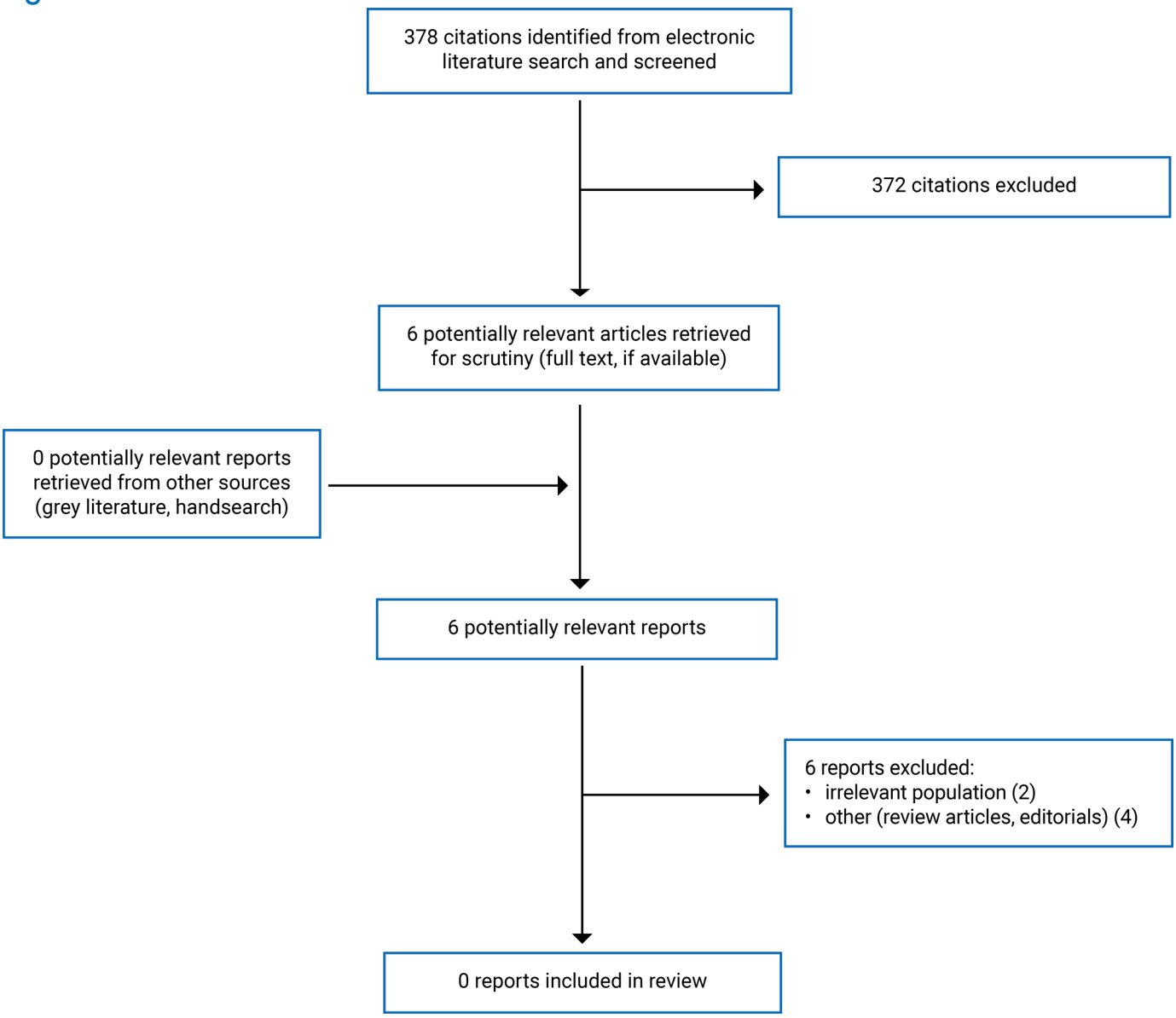
Appendix 1: Selection of Included Studies

Figure 1: Selection of Included Studies



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