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Cancer Immunotherapy After Adjuvant Immunotherapy: Clinical Effectiveness and Guidelines

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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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Research Questions

1. What is the clinical effectiveness of nivolumab, pembrolizumab, or ipilimumab-nivolumab in patients with melanoma who progressed after adjuvant therapy with nivolumab or pembrolizumab?
2. What is the clinical effectiveness of atezolizumab, nivolumab or pembrolizumab in patients with recurrent/metastatic non-small cell lung cancer (NSCLC) who progressed after consolidation therapy with durvalumab?
3. What are the evidence-based guidelines on the timing of retreatment with immune checkpoint inhibitors?

Key Findings

No relevant clinical evidence was identified regarding the clinical effectiveness of nivolumab, pembrolizumab, or ipilimumab-nivolumab in patients with melanoma who progressed after adjuvant therapy with nivolumab or pembrolizumab. No relevant clinical evidence was identified regarding the clinical effectiveness of atezolizumab, nivolumab or pembrolizumab in patients with recurrent/metastatic non-small cell lung cancer (NSCLC) who progressed after consolidation therapy with durvalumab. Additionally, no relevant evidence-based guidelines were identified regarding the timing of retreatment with immune checkpoint inhibitors.

Methods

A limited literature search was conducted by an information specialist on key resources including Ovid Medline, the Cochrane Library, the University of York Centre for Reviews and Dissemination (CRD) databases, the websites of Canadian and major international health technology agencies, as well as a focused Internet search. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were immune-oncology drugs and melanoma or non-small cell lung cancer. Search filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, or network meta-analyses, randomized controlled trials or controlled clinical trials or guidelines. An additional focused search on the timing of retreatment was also conducted. No filters were applied to the focused search to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2014 and July 26, 2019. Internet links were provided, where available.

Selection Criteria

One reviewer screened citations and selected studies based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Q1: Patients with metastatic melanoma who completed and have progressed after adjuvant therapy with nivolumab or pembrolizumab Q2: Patients with recurrent/metastatic non-small cell lung cancer (NSCLC) who completed and have progressed after consolidation therapy with durvalumab
Intervention	Q1: Nivolumab, pembrolizumab, ipilimumab combined with nivolumab Q2: Atezolizumab Nivolumab, pembrolizumab
Comparator	Q1-Q2: Any comparator (e.g., placebo, immunotherapy, chemotherapy, targeted therapy) No treatment (i.e., single arm studies) Q3: Evidence-based guidelines
Outcomes	Q1-Q2: Progression-free survival, overall survival, response rate, quality of life Adverse events, discontinuation Length of treatment-free period prior to intervention Q3: Evidence-based guidelines
Study Designs	Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies, evidence-based guidelines

Results

Rapid Response reports are organized so that the higher quality evidence is presented first. Therefore, health technology assessment reports, systematic reviews, and meta-analyses are presented first. These are followed by randomized controlled trials, non-randomized studies, and evidence-based guidelines.

No relevant health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, or non-randomized studies were identified regarding the clinical effectiveness of nivolumab, pembrolizumab, or ipilimumab-nivolumab in patients with melanoma who progressed after adjuvant therapy with nivolumab or pembrolizumab. No relevant health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, or non-randomized studies were identified regarding the clinical effectiveness or atezolizumab, nivolumab or pembrolizumab in patients with recurrent/metastatic non-small cell lung cancer (NSCLC) who progressed after consolidation therapy with durvalumab. Additionally, relevant evidence-based guidelines were identified regarding the timing of retreatment with immune checkpoint inhibitors.

References of potential interest are provided in the appendix.

Health Technology Assessments

No literature identified.

Systematic Reviews and Meta-analyses

No literature identified.

Randomized Controlled Trials

No literature identified.

Non-Randomized Studies

No literature identified.

Guidelines and Recommendations

No literature identified.

Appendix — Further Information

Systematic Reviews and Meta-Analyses – Adjuvant or Consolidation Therapy Unspecified

1. Crequit P, Chaimani A, Yavchitz A, et al. Comparative efficacy and safety of second-line treatments for advanced non-small cell lung cancer with wild-type or unknown status for epidermal growth factor receptor: a systematic review and network meta-analysis. *BMC Med*. 2017 10 30;15(1):193.
PubMed: PM29082855

2. Huang J, Zhang Y, Sheng J, et al. The efficacy and safety of nivolumab in previously treated advanced non-small-cell lung cancer: a meta-analysis of prospective clinical trials. *Onco Targets Ther*. 2016;9:5867-5874.
PubMed: PM27713640

3. Melosky B, Chu Q, Juergens R, Leighl N, McLeod D, Hirsh V. Pointed progress in second-line advanced non-small-cell lung cancer: the rapidly evolving field of checkpoint inhibition. *J Clin Oncol*. 2016 05 10;34(14):1676-1688.
PubMed: PM26884577

Randomized Controlled Trials

Alternative Population – Previously Treated with Ipilimumab

4. Schadendorf D, Dummer R, Hauschild A, et al. Health-related quality of life in the randomised KEYNOTE-002 study of pembrolizumab versus chemotherapy in patients with ipilimumab-refractory melanoma. *Eur J Cancer*. 2016 11;67:46-54.
PubMed: PM27596353

Adjuvant or Consolidation Therapy Unspecified

5. Weis TM, Hough S, Reddy HG, Daignault-Newton S, Kalemkerian GP. Real-world comparison of immune checkpoint inhibitors in non-small cell lung cancer following platinum-based chemotherapy. *J Oncol Pharm Pract*. 2019 Jun 25:1078155219855127.
PubMed: PM31238808

6. Leighl NB, Hellmann MD, Hui R, et al. Pembrolizumab in patients with advanced non-small-cell lung cancer (KEYNOTE-001): 3-year results from an open-label, phase 1 study. *Lancet Respir Med*. 2019 Apr;7(4):347-357.
PubMed: PM30876831

7. Weber JS, Gibney G, Sullivan RJ, et al. Sequential administration of nivolumab and ipilimumab with a planned switch in patients with advanced melanoma (CheckMate 064): an open-label, randomised, phase 2 trial. *Lancet Oncol*. 2016 Jul;17(7):943-955.
PubMed: PM27269740

8. Fehrenbacher L, Spira A, Ballinger M, et al. Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (POPLAR): a multicentre, open-label, phase 2 randomised controlled trial. *Lancet*. 2016 Apr 30;387(10030):1837-1846.
PubMed: PM26970723

Non-Randomized Studies

Adjuvant Therapy Unspecified

9. Ribeiro Gomes J, Schmerling RA, Haddad CK, et al. Analysis of the abscopal effect with anti-PD1 therapy in patients with metastatic solid tumors. *J Immunother*. 2016 Nov/Dec;39(9):367-372.
PubMed: PM27741091

Review Articles

10. La-Beck NM, Jean GW, Huynh C, Alzghari SK, Lowe DB. Immune checkpoint inhibitors: new insights and current place in cancer therapy. *Pharmacotherapy*. 2015 Oct;35(10):963-976.
PubMed: PM26497482

Additional References

11. Owen CN, Larkin JMG, Shoushtari AN, et al. A multicenter analysis of melanoma recurrence following adjuvant anti-PD1 therapy. *J Clin Oncol*. 2019;37(15_suppl):9502-9502.
https://ascopubs.org/doi/abs/10.1200/JCO.2019.37.15_suppl.9502