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CADTH RAPID RESPONSE REPORT:
SUMMARY WITH CRITICAL APPRAISAL

Immune Checkpoint Inhibitors for Classical Hodgkin Lymphoma in Brentuximab Vedotin-naïve Patients: A Review of Clinical Effectiveness, Cost-Effectiveness, and Guidelines

Service Line:	Rapid Response Service
Version:	1.0
Publication Date:	June 21, 2019
Report Length:	16 Pages

CADTH

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Cite As: Immune Checkpoint Inhibitors for Classical Hodgkin's Lymphoma in Brentuximab Vedotin-naïve Patients: A Review of Clinical Effectiveness, Cost-Effectiveness, and Guidelines. Ottawa: CADTH; 2019 Jun. (CADTH rapid response report: summary with critical appraisal).

ISSN: 1922-8147 (online)

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Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

Abbreviations

SCT	stem cell therapy/transplantation
NCCN	National Comprehensive Cancer Network
RCT	randomized controlled trial

Context and Policy Issues

Hodgkin lymphoma is a rare form of cancer that affects the white blood cells of the lymphatic system.[1] Across Canada, an estimated 1000 new cases of Hodgkin lymphoma are diagnosed each year with more than 70% occurring in patients younger than 55 years.[2]

Prognosis is generally dependent on the stage at which Hodgkin lymphoma is diagnosed and treated.[1] Early Hodgkin lymphoma refers to the disease in stages 1 and 2, while advanced Hodgkin lymphoma refers to the disease in stages 2B, 3 and 4.[1] The average 5-year relative survival rate in Canada is higher than 90% for patients diagnosed with stages 1 and 2 Hodgkin lymphoma and 65% for those diagnosed with stage 4 Hodgkin lymphoma.[1] Approximately 95% of cases are classified as classical Hodgkin lymphoma which manifests in a variety of forms, namely, nodular sclerosis, mixed cellularity, lymphocyte-rich and lymphocyte-depleted Hodgkin lymphoma.[1] The remaining 5% of cases are classified as nodular lymphocyte-predominant Hodgkin lymphoma.[1]

Treatment options vary with the type and stage of Hodgkin lymphoma as well as with the patient's age and overall health.[1] The first line of treatment is typically chemotherapy followed by radiotherapy, although in cases where Hodgkin lymphoma is localized, radiation may be administered as first line therapy. Second-line therapy may include autologous stem cell therapy or transplantation (auto-SCT), allogeneic stem cell therapy or transplantation (allo-SCT), anti-CD30 antibodies (such as brentuximab vedotin), and anti-CD20 antibodies (such as rituximab). For those whose cancer does not adequately respond to second-line therapy, those who do not have access to therapies like brentuximab vedotin, or those who are ineligible for SCT, immune checkpoint inhibitors (such as nivolumab and pembrolizumab) may be potential options.[3]

This review aims to summarize the evidence regarding the clinical effectiveness and cost-effectiveness of immune checkpoint inhibitors in brentuximab vedotin-naïve patients with classical Hodgkin lymphoma who either failed or are not eligible for auto-SCT. The review also aims to summarize relevant evidence-based guidelines.

Research Questions

1. What is the clinical effectiveness of immune checkpoint inhibitors in brentuximab vedotin-naïve, classical Hodgkin lymphoma patients who failed autologous stem cell transplantation?
2. What is the cost-effectiveness of immune checkpoint inhibitors in brentuximab vedotin-naïve, classical Hodgkin lymphoma patients who failed autologous stem cell transplantation?

3. What is the clinical effectiveness of immune checkpoint inhibitors in brentuximab vedotin-naïve classical Hodgkin lymphoma patients who are not eligible for autologous stem cell transplantation?
4. What is the cost-effectiveness of immune checkpoint inhibitors in brentuximab vedotin-naïve classical Hodgkin lymphoma patients who are not eligible for autologous stem cell transplantation?
5. What are the evidence-based guidelines regarding the use of immune checkpoint inhibitors in brentuximab vedotin-naïve classical Hodgkin lymphoma patients?

Key Findings

The evidence on the treatment of Hodgkin Lyphoma in brentuximab vedotin-naïve patients with immune checkpoint inhibitors is sparse.

One set of evidence-based guidelines was found that provided recommendations on diagnosing, treating, and following patients with early stage, intermediate stage, or advanced stage classical Hodgkin lymphoma. Based on evidence of limited quality, quantity, and consistency, the guidelines recommend treating eligible adults with immune checkpoint inhibitors such as nivolumab and pembrolizumab for relapsed or refractory Hodgkin lymphoma following autologous hematopoietic stem cell transplantation with or without brentuximab vedotin. Of note, the recommendation was not specific to brentuximab vedotin-naïve patients and sections of the guideline document remain under development. The guidelines indicated that immune checkpoint inhibitors may be considered as an option for patients who are ineligible for stem cell transplantation due to comorbidity or failed second-line chemotherapy. Nivolumab and pembrolizumab may also be used for patients following allogeneic stem cell transplantation. Guidance was provided suggesting that nivolumab and pembrolizumab may be offered as palliative therapy options for patients older than 60 years who were previously treated with brentuximab vedotin.

The authors followed established processes for developing the guidelines, however there were some gaps in reporting that made it challenging to assess all aspects of the development processes. The guidelines were written for the United States population and as such may not be applicable to the Canadian population. There was no relevant primary evidence regarding the clinical effectiveness or cost-effectiveness of immune checkpoint inhibitors in brentuximab vedotin-naïve patients who either had failed or were not eligible for auto-SCT.

Methods

Literature Search Methods

A limited literature search was conducted by an information specialist on key resources including MEDLINE via Ovid, EMBASE via Ovid, 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 nivolumab or pembrolizumab and Hodgkins Lymphoma. No filters were applied 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 May 26, 2019.

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

Population	Q1-Q2: Adults with relapsed or refractory classical Hodgkin lymphoma after autologous stem cell transplantation and who were never treated with brentuximab vedotin Q3-Q4: Adults with relapsed or refractory classical Hodgkin lymphoma who are not eligible for autologous stem cell transplantation and who were never treated with brentuximab vedotin Q5: Adults with relapsed or refractory classical Hodgkin lymphoma who were never treated with Brentuximab vedotin
Intervention	Immune checkpoint inhibitors (i.e., nivolumab, pembrolizumab)
Comparators	Q1 to Q5: • Nivolumab, pembrolizumab • Brentuximab vedotin • Chemotherapy (e.g., gemcitabine, vinorelbine) • Best supportive care (i.e., palliative care or other forms of care that assist with concomitant needs)
Outcomes	Q1 & Q3: Progression-free survival, overall survival, response rate, quality of life, adverse events, discontinuation Q2 & Q4: Cost-effectiveness Q5: Evidence-based guidelines
Study Designs	Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies, economic evaluations, guidelines

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2014. Guidelines with unclear methodology were also excluded.

Critical Appraisal of Individual Studies

The included guidelines were critically appraised by one reviewer using the AGREE II instrument.[4] Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 260 citations were identified in the literature search. Following screening of titles and abstracts, 250 citations were excluded and 10 potentially relevant reports from the electronic search were retrieved for full-text review. Three potentially relevant publications were retrieved from the grey literature search and other sources for full text review. Of

these 13 potentially relevant articles, 12 publications were excluded for various reasons, and 1 publication met the inclusion criteria for this report. Appendix 1 presents the PRISMA[5] flowchart of the study selection.

Additional references of potential interest are provided in Appendix 5.

Summary of Study Characteristics

Study characteristics are summarized below and details are available in Appendix 2.

Study Design

No relevant clinical effectiveness and cost-effectiveness studies were found.[6] However, one relevant set of guidelines was identified that was published by the National Comprehensive Cancer Network (NCCN).[7] The NCCN guidelines were developed as an update to version 3.2018 of the NCCN Guidelines for Hodgkin lymphoma following a search of the Pubmed database for articles published between May 2015 and July 2016. Results were limited to phase II to IV clinical trials, randomized controlled trials (RCTs), meta-analyses, systematic reviews, and validation studies. Articles deemed to be relevant by the Hodgkin lymphoma guideline update panel were considered. According to the generic development process[6] the NCCN guidelines development panels consist of multidisciplinary, disease-specific sub-specialists who were both clinicians and researchers, as well as a patient advocate and a primary care physician, at minimum. The recommendation statements are classified according to the level of evidence on which they are based and the degree of consensus within the guideline panel.[6] The level of evidence is determined by the quality of data (i.e., the type of studies included), the quantity of data included in the studies, and consistency across the body of evidence. The degree of consensus is determined by the percentage of panel votes and categorized as “uniform NCCN consensus” if at least 85 percent of the panelists are in favour of the recommendation and “NCCN consensus” if less than 85 percent but at least 50 percent are in favour. “Major disagreement” is indicated when there is disagreement regarding the appropriateness of the intervention but at least 25 percent of the panel are in favour of the recommendation. The guidelines are reviewed by multidisciplinary faculty at each NCCN Member Institution. The authors noted that while the update to the Hodgkin lymphoma guideline has been published, the discussion section remains under development.

Country of Origin

The NCCN guidelines were developed in the United States.[7]

Patient Population

The guidelines covered patients with classical, nodular lymphocyte-predominant, and recurrent or refractory Hodgkin lymphoma. The guidelines were not limited to brentuximab-naïve patients.

Interventions and Comparators

The treatment options that were considered included chemotherapy, radiotherapy, stem cell therapy, brentuximab vedotin, rituximab, nivolumab and pembrolizumab.

Outcomes

The outcomes of interest included recurrence or progression-free survival, overall survival, and therapy-related late sequelae, including but not limited to, hyperthyroidism, myelosuppression, infertility, and pulmonary toxicity.

Summary of Critical Appraisal

The following domains from the AGREE II instrument[4] were appraised: scope and purpose, stakeholder involvement, rigour of development, clarity of presentation, applicability, and editorial independence. Additional details regarding the strengths and limitations of included publications are provided in Appendix 3.

There were multiple strengths that suggest that the development process was rigorous: systematic methods were used to search for evidence, the strengths and limitations of the body of evidence were outlined, and the health benefits, side effects and risks of various treatment methods were considered. The authors also clearly presented different options for management of Hodgkin lymphoma ensuring that the targeted users were aware of alternative clinical pathways. While not explicitly described, the objectives were evident – that is, the guidelines were written for the diagnosis, treatment and follow-up of patients with Hodgkin lymphoma. The structure of the guideline development group, review procedures, and the target users were described comprehensively in the NCCN's generic procedure document. The criteria for selecting evidence, methods for formulating the recommendations, and a process for updating the guidelines, were also described in the generic procedure. By citing generic procedures, the authors did not allow for aspects that were unique to the development of the Hodgkin lymphoma guidelines to be critically appraised.

The weaknesses that were found as part of the critical appraisal were primarily limited to applicability: the authors did not describe facilitators and barriers to the application of their guidelines nor did they provide advice specific to implementation, monitoring, and auditing the guidelines. Without information on applicability, it is challenging to assess potential implementation aspects. The authors also did not provide conflict of interest statements nor evidence that the views and the preferences of the target population were sought. Conflict of interest statements would facilitate a critical assessment of the risk that one or more groups may have had opportunities to exert undue influence over the recommendations. As the guidelines currently stand, it is not possible to determine whether competing interests existed among the authors and reviewers, and as such, whether the views of the funding body or any other group may have influenced the content of the guidelines. Although the key recommendations were easily identifiable, certain aspects of the recommendation statements were ambiguous, such as, the sequence in which treatment options were to be considered. In addition, the authors included options for treatment without explicitly indicating whether these options were recommended. Finally, while the generic guideline procedure suggests that recommendations are reviewed by individuals representing a diverse group of member institutions, details of the expert review process specific to the guidelines on Hodgkin lymphoma were missing.

Summary of Findings

Appendix 4 presents a table of the main study findings and authors' conclusions.

Clinical effectiveness of immune checkpoint inhibitors in brentuximab vedotin-naïve, classical Hodgkin lymphoma patients who failed autologous stem cell transplantation

No relevant evidence was identified; therefore, no summary can be provided.

Cost-effectiveness of immune checkpoint inhibitors in brentuximab vedotin-naïve, classical Hodgkin lymphoma patients who failed autologous stem cell transplantation

No relevant evidence was identified; therefore, no summary can be provided.

Clinical effectiveness of immune checkpoint inhibitors in brentuximab vedotin-naïve, classical Hodgkin lymphoma patients who are not eligible for autologous stem cell transplantation

No relevant evidence was identified; therefore, no summary can be provided.

Cost-effectiveness of immune checkpoint inhibitors in brentuximab vedotin-naïve, classical Hodgkin lymphoma patients who are not eligible for autologous stem cell transplantation

No relevant evidence was identified; therefore, no summary can be provided.

Evidence-based guidelines regarding the use of immune checkpoint inhibitors in Brentuximab vedotin-naïve classical Hodgkin lymphoma patients

Based on low-level evidence, the NCCN guideline panel recommends the use of nivolumab and pembrolizumab in “any adults aged 18 years or older with [classical Hodgkin lymphoma] that has relapsed or progressed after autologous hematopoietic stem cell transplant ± Brentuximab vedotin” (page 28).[7] The guidelines do not provide unique guidance for the use of immune checkpoint inhibitors in brentuximab vedotin-naïve patients. Of note, the discussion statement that is relevant to the recommendation is currently under review and reads “Nivolumab and pembrolizumab are included as additional therapy options for classical Hodgkin lymphoma patients that have relapsed or progressed following high-dose therapy or auto-SCT and post-transplant brentuximab vedotin” (page MS-28).[7]

The guidelines indicate that checkpoint inhibitors may also be an option for adults with relapsed or refractory classical Hodgkin lymphoma who are ineligible for transplantation due to comorbidities or failure of second-line chemotherapy. Based on two studies, the guidelines state that nivolumab and pembrolizumab may be used following allogeneic transplantation. The authors indicated that prior to allogeneic transplantation caution must be observed when considering immune checkpoint inhibitors because of the increased risk of graft-to-host disease and other immunologic complications. These statements were not explicitly reported as recommendations.

For adults older than 60 years, the NCCN guidelines indicate that while no uniform recommendations can be made, nivolumab and pembrolizumab may be offered as palliative therapy options in patients previously treated with brentuximab vedotin. The authors did not outline the details of prior therapy.

Limitations

The relevant literature on Hodgkin lymphoma consisted of one set of guidelines that included recommendations for adults who had relapsed or progressed. The discussion section of the guidelines document is still under production; as such caution is warranted in making conclusions about the guidelines. Overall, the authors followed established processes for developing the guidelines, however there were some gaps in reporting that made it challenging to assess aspects that were unique to the development of the Hodgkin lymphoma guidelines. The recommendations were written for the United States population and as such may not be generalizable to the Canadian population.

Conclusions and Implications for Decision or Policy Making

There was no primary evidence regarding the clinical effectiveness or cost-effectiveness of immune checkpoint inhibitors for brentuximab vedotin-naïve adults with relapsed or refractory classical Hodgkin lymphoma, irrespective of eligibility for or prior history of autologous stem cell transplantation.

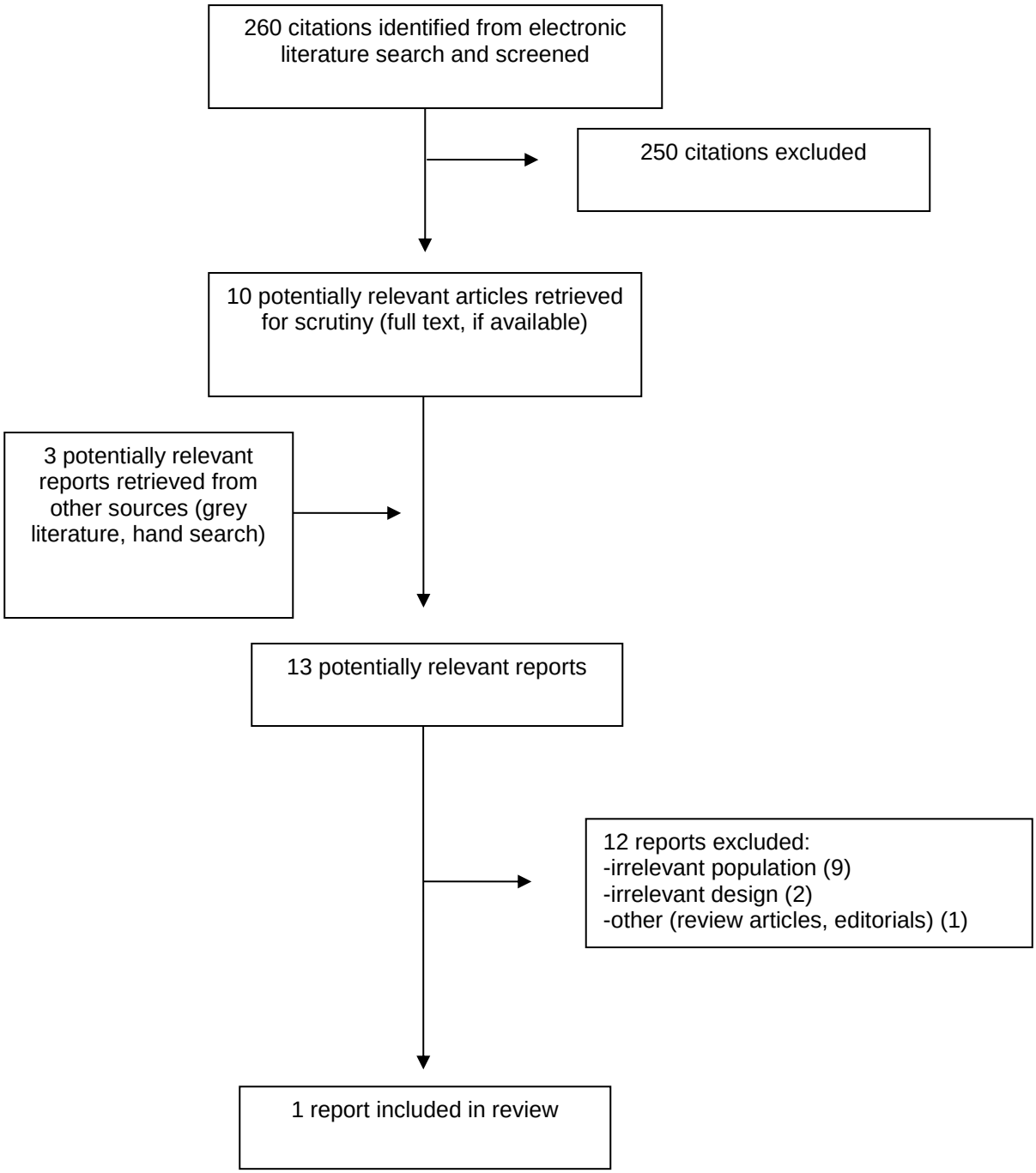
One set of guidelines were identified that included recommendations for diagnosing, treating, and following patients with classical Hodgkin lymphoma. Regarding treatment, the guidelines recommend treating eligible adults with immune checkpoint inhibitors such as nivolumab and pembrolizumab for relapsed or refractory Hodgkin lymphoma following autologous hematopoietic stem cell transplantation with or without brentuximab vedotin. Immune checkpoint inhibitors may be considered as an option for patients who are ineligible for stem cell transplantation due to comorbidity or failed second-line chemotherapy. Nivolumab and pembrolizumab may also be used for patients following allogeneic stem cell transplantation. Guidance was provided suggesting that nivolumab and pembrolizumab may be offered as palliative therapy options for patients older than 60 years who were previously treated with brentuximab vedotin.

Canadian policy-makers may want to consider that the relevant recommendation and guidance statements were based on low-level evidence. Furthermore, the guidelines were written for patients being treated within the United States' healthcare system and as such may not be generalizable to the Canadian population.

References

1. Canadian Cancer Society. What is Hodgkin lymphoma? 2019: http://www.cancer.ca/en/cancer-information/cancer-type/hodgkin-lymphoma/hodgkin-lymphoma/?region=on. Accessed 2019 Jun 21.
2. Xie L, Semenciw R, Mery L. Chapter 4: Cancer incidence in Canada: trends and projections (1983-2032) – Hodgkin lymphoma. *Health Promotion and Chronic Disease Prevention in Canada: Research, Policy and Practice.* 2015;35(Suppl 1). https://www.canada.ca/en/public-health/services/reports-publications/health-promotion-chronic-disease-prevention-canada-research-policy-practice/vol-35-no-1-2015/supplement/page-13.html Accessed 2019 Jun 21.
3. Scott LJ. Brentuximab Vedotin: A Review in CD30-Positive Hodgkin Lymphoma. *Drugs.* 2017;77(4):435-445.
4. Agree Next Steps Consortium. The AGREE II Instrument. [Hamilton, ON]: AGREE Enterprise; 2017: https://www.agreetrust.org/wp-content/uploads/2017/12/AGREE-II-Users-Manual-and-23-item-Instrument-2009-Update-2017.pdf. Accessed 2019 Jun 21.
5. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *J Clin Epidemiol.* 2009;62(10):e1-e34.
6. Development and Update of the NCCN Guidelines. Plymouth Meeting (PA): National Comprehensive Cancer Network; 2019: https://www.nccn.org/professionals/development.aspx. Accessed 2019 Jun 21.
7. Hodgkin Lymphoma. Version 1.2019. *(NCCN Clinical Practice Guidelines in Oncology)*. Plymouth Meeting (PA): National Comprehensive Cancer Network; 2019: www.nccn.org. Accessed 2019 Jun 21.

Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Guidelines

Intended Users, Target Population, Country	Intervention and Practice Considered	Major Outcomes Considered	Evidence Collection, Selection, and Synthesis	Evidence Quality Assessment	Recommendations Development and Evaluation	Guideline Validation
National Comprehensive Cancer Network, 2019[7]						
Physicians, nurses, pharmacists, payers, patients and their families, the United States	Management of Hodgkin lymphoma	Recurrence or progression-free survival, overall survival, and therapy-related late sequelae, including but not limited to, hyperthyroidism, myelosuppression, infertility, and pulmonary toxicity	A search of the Pubmed database for articles published between May 2015 and July 2016; phase II to IV clinical trials, RCTs, meta-analyses, systematic reviews, and validation studies. Guideline panel selected relevant articles.	The level of evidence incorporated: study design, quantity of data, and consistency of data	Recommendations were developed according to a standard process by a panel of clinicians, researchers, and patient advocates.	The guidelines are reviewed by multidisciplinary faculty at each National Comprehensive Cancer Network Member Institution.

RCT = randomized controlled trial

Appendix 3: Critical Appraisal of Included Publications

Table 3: Strengths and Limitations of Guidelines using AGREE II[4]

Item	Guideline
	NCCN, 2019[7]
Domain 1: Scope and Purpose	
1. The overall objective(s) of the guideline is (are) specifically described.	+/-
2. The health question(s) covered by the guideline is (are) specifically described.	+/-
3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.	+
Domain 2: Stakeholder Involvement	
4. The guideline development group includes individuals from all relevant professional groups.	+[a]
5. The views and preferences of the target population (patients, public, etc.) have been sought.	-
6. The target users of the guideline are clearly defined.	+[a]
Domain 3: Rigour of Development	
7. Systematic methods were used to search for evidence.	+
8. The criteria for selecting the evidence are clearly described.	+[a]
9. The strengths and limitations of the body of evidence are clearly described.	+
10. The methods for formulating the recommendations are clearly described.	+[a]
11. The health benefits, side effects, and risks have been considered in formulating the recommendations.	+
12. There is an explicit link between the recommendations and the supporting evidence.	+
13. The guideline has been externally reviewed by experts prior to its publication.	?
14. A procedure for updating the guideline is provided.	+[a]
Domain 4: Clarity and Presentation	
15. The recommendations are specific and unambiguous.	-
16. The different options for management of the condition or health issue are clearly presented.	+
17. Key recommendations are easily identifiable.	+
Domain 5: Applicability	
18. The guideline describes facilitators and barriers to its application.	-

Table 3: Strengths and Limitations of Guidelines using AGREE II[4]

Item	Guideline
19. The guideline provides advice and/or tools on how the recommendations can be put into practice.	-
20. The potential resource implications of applying the recommendations have been considered.	-
21. The guideline presents monitoring and/or auditing criteria.	-
Editorial Independence	
22. The views of the funding body have not influenced the content of the guideline.	?
23. Competing interests of guideline development group members have been recorded and addressed.	?

+ = yes; - = no; +/- = partially; ? = unclear; NCCN = National Comprehensive Cancer Network

[a] As described in the generic development process guide

Appendix 4: Main Study Findings and Authors' Conclusions

Table 4: Summary of Recommendations in Included Guidelines

Recommendations	Strength of Evidence and Recommendations
NCCN, 2019[7]	
Multiple recommendations were made for using Nivolumab and pembrolizumab to treat any adults aged 18 years or older: 1. "with [classical Hodgkin lymphoma] if they relapsed or progressed following autologous hematopoietic stem cell transplant ± Brentuximab vedotin" (p 28) 2. as an option for relapsed or refractory classical Hodgkin lymphoma when ineligible for transplantation due to comorbidities or failure of second-line chemotherapy 3. following allogeneic transplantation 4. with caution prior to allogeneic transplantation immune because of the increased risk of graft-to-host disease and other immunologic complications. For adults older than 60 years, the NCCN guidelines indicate that nivolumab and pembrolizumab may be offered as palliative therapy options.	The recommendation was classified as category 2A suggesting that it was based on low-level evidence

NCCN = National Comprehensive Cancer Network

Appendix 5: Additional References of Potential Interest

A cost-effectiveness analysis based on a mixed patient population

Large S, Hettle R, Balakumaran A, Wu E, Borse RH. Cost-effectiveness of pembrolizumab versus brentuximab vedotin for patients with relapsed or refractory classical Hodgkin's lymphoma: a United States payer perspective. *J Med Econ*. 2018 Nov 13:1-10.

Clinical studies with mixed patient populations

Armand P, Engert A, Younes A, et al. Nivolumab for Relapsed/Refractory Classic Hodgkin Lymphoma After Failure of Autologous Hematopoietic Cell Transplantation: Extended Follow-Up of the Multicohort Single-Arm Phase II CheckMate 205 Trial. *J Clin Oncol*. 2018 May 10;36(14):1428-1439.

Chen R, Zinzani PL, Fanale MA, et al. Phase II Study of the Efficacy and Safety of Pembrolizumab for Relapsed/Refractory Classic Hodgkin Lymphoma. *J Clin Oncol*. 2017 Jul 01;35(19):2125-2132.

von Tresckow B, Fanale M, Ardeshna KM, et al. Patient-reported outcomes in KEYNOTE-087, a phase 2 study of pembrolizumab in patients with classical Hodgkin lymphoma. *Leuk Lymphoma*. 2019 Apr 23:1-7.