CADTH | pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Clinical Guidance Report

Nivolumab (Opdivo) for Classical Hodgkin Lymphoma

May 3, 2018

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1 GUIDANCE IN BRIEF

This Clinical Guidance Report was prepared to assist the pCODR Expert Review Committee (pERC) in making recommendations to guide funding decisions made by the provincial and territorial Ministries of Health and provincial cancer agencies regarding nivolumab (Opdivo) for classical Hodgkin's Lymphoma (cHL). The Clinical Guidance Report is one source of information that is considered in the *pERC Deliberative Framework*. The *pERC Deliberative Framework* is available on the CADTH website (www.cadth.ca/pcodr).

This Clinical Guidance is based on: a systematic review of the literature regarding nivolumab (Opdivo) for cHL conducted by the Lymphoma Clinical Guidance Panel (CGP) and the pCODR Methods Team; input from patient advocacy groups; input from the Provincial Advisory Group; input from Registered Clinicians; and supplemental issues relevant to the implementation of a funding decision.

The systematic review and supplemental issues are fully reported in Sections 6 and 7. A background Clinical Information provided by the CGP, a summary of submitted Patient Advocacy Group Input on nivolumab (Opdivo) for cHL, a summary of submitted Provincial Advisory Group Input on nivolumab (Opdivo) for cHL, and a summary of submitted Registered Clinician Input on nivolumab (Opdivo) for cHL, and are provided in Sections 2, 3, 4, and 5 respectively.

1.1 Introduction

The objective of this review is to evaluate the effectiveness and safety of nivolumab (Opdivo) for classical Hodgkin Lymphoma (cHL) that has relapsed or progressed after (1) autologous stem cell transplantation (ASCT) and brentuximab vedotin (BV), OR (2) 3 or more lines of systemic therapy including ASCT.

Nivolumab (Opdivo) is an immunotherapy (monoclonal antibody) that targets the programmed cell death-1 receptor (PD-1) and inhibits the PD-1 pathway. Nivolumab has a Health Canada indication that reflects the requested patient population for reimbursement. Nivolumab has been issued marketing authorization with conditions (NOC/c) for cHL that has relapsed or progressed after:

(1) autologous stem cell transplantation (ASCT) and brentuximab vedotin, or
(2) 3 or more lines of systemic therapy including ASCT.

The Health Canada Product Monograph also noted that an improvement in survival or disease-related symptoms has not yet been established.

Of note, the patient subgroup referred to in point (1) aligns with cohorts B and C of the CHECKMATE-205 trial. The patient subgroup in point (2) aligns with cohort A of the CHEKCKMATE-205 trial. For further details on the cohorts A, B and C please see section 1.2.1 below.

The recommended dose is 3 mg/kg administered intravenously over 60 minutes every 2 weeks. As per product monograph, nivolumab treatment should be continued as long as a clinical benefit is observed or until treatment is no longer tolerated by the patient.

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

The pCODR systematic review included two nonrandomized trials. The results of CHECKMATE-205 (N = 243) and CHECKMATE-039 (N=23) will be presented below:

CHECKMATE-205[1,2]

CHECKMATE-205 was a non-comparative, multi-cohort, single-arm, open-label, phase 2 study of nivolumab in patients with classical Hodgkin Lymphoma (cHL), after failure of autologous stem cell transplant (ASCT), that was conducted in 10 countries in Europe and North America, including Canada.

Patients were studied in four cohorts with respect to the status of their previous BV treatment: patients who had failed on ASCT and were BV-naïve (**Cohort A; n = 63**); patients who had relapsed or failed on BV treatment as a salvage therapy after failure of ASCT (**Cohort B; n = 80**); patients who had ASCT and BV in any treatment order (i.e. BV before ASCT, and/or after ASCT) (**Cohort C; n = 100**); and those who had newly diagnosed and untreated advanced stage cHL **(Cohort D)**. This pCODR review will only present the efficacy and safety results from cohorts A, B and C because cohort D is not aligned with the funding request, and is therefore, beyond the scope of this review.

Cohorts A, B and C align with the following patient subgroups in the funding request:

Patient with cHL that has relapsed or progressed after:

(1) ASCT and brentuximab vedotin, or
(2) 3 or more lines of systemic therapy including ASCT.

The patient group in point (1) is aligned with CheckMate-205 (CM205) Cohort B and Cohort C. The patient group in point (2) is aligned with CM205 Cohort A.

The trial included adult patients who had failed or progressed after ASCT, had an Eastern Cooperative Oncology Group performance (ECOG) status score of 0 or 1, and either documented failure to achieve at least partial remission after the most recent treatment, or documented relapse or disease progression. Patients also had to have received previous high-dose conditioning chemotherapy followed by ASCT as part of salvage therapy.

Patients in Cohorts A, B, and C were treated with nivolumab 3 mg/kg, intravenously, every 2 weeks until unacceptable toxicity or disease progression or progressive disease according to the International Working Group criteria for Malignant Lymphoma (2007 IWG) criteria.

The primary endpoint was objective response rate (ORR), determined by an Independent Radiologic Review Committee (IRRC). Secondary study outcomes included duration of objective response (DOR), complete remission (CR) rate, duration of CR, partial remission (PR) rate, duration of PR, and progression-free survival (PFS) based on IRRC assessments; ORR, DOR, and PFS based on investigator assessments, overall survival (OS), safety, quality of life (QoL). Efficacy and safety analyses were performed in patients who had received at least one dose of nivolumab. The analysis for the primary outcome was performed independently for each cohort after completion of a pre-specified duration of minimum follow-up (9 months for Cohort A, and 6 months for Cohort B and Cohort C).

Efficacy

The key efficacy outcomes of CHECKMATE-205 trial are presented in Table 1.1. As of the December 2016 database lock, ORR was achieved in 65% of patients in Cohort A, 68% of patients in Cohort B, and 73% of patients in Cohort C. Complete remission was achieved in 29%, 13%, and 12% of patients in Cohorts A, B, and C, respectively.[2] The median duration of IRRC-assessed objective response reached 20 months (95% CI 13 – 20) in Cohort A, 16 months (95% CI 8 – 20) in Cohort B, and 15 months (95% CI 9 – 17) in Cohort C.

The median IRRC-assessed PFS rates were 18.0 months (95% CI 11 - 22) in cohort A, 15 months (95% CI 11 - 20) in cohort B, and 12 months (95% CI 11 - 18) in Cohort C.[2] As of 16-Dec-2016 data cut-off date, the median OS was not reached in none of the study cohorts.[2] The analysis of survival data from this data cut-off date showed that after a median follow-up 19.12 months the OS rate was 93.4% in Cohort A; after a median follow-up 22.70 months the OS rate was 89.2% in Cohort B; and after a median follow-up 16.16 months the OS rate was 88.7% in Cohort C.[3]

Quality of life

In Cohort B, by week 33, 58% of patients had at least one post-baseline EORTC QLQ-C30 or EQ-5D assessment. Least squares mean score change from baseline at week 33 was 19.1 (±3.1) for EQ-5D VAS and 7.6 (±2.3) for the EORTC QLQ-C30 global health/quality of life status scale.[1,4] When the data were pooled for Cohorts A, B, and C, nivolumab treatment resulted in clinically meaningful and statistically significant improvement in general and cancer-specific patient related outcomes. Improvement started early (Week 9) and persisted to Week 93.[5]

Harms

As of December 2016 data cut-off, the most common drug-related AEs in 243 nivolumab-treated patients (Cohorts A, B, and C) included fatigue (23%), diarrhea (15%), and infusion reactions (14%). The most common drug-related serious AEs were infusion reactions (2%) and pneumonitis (1%). Serious AEs included fatigue (1%), diarrhea (1%), rash (1%), infusion reactions (<1%), and autoimmune hepatitis (1%). The most common drug-related AEs which led to discontinuation of the study treatment were pneumonitis (2%) and autoimmune hepatitis (1%).[2]

Table 1.1: Highlights of Key Efficacy Outcomes of CHECKMATE-205 Trial

Treatment groups	CHECKMATE-205			
	Cohort A (n = 63)	Cohort B (n = 80)	Cohort C (n = 100)	All patients (N = 243)
Primary Outcome				
ORR as assessed by IRRC[ab] %, (95% CI)	65 (52–77)	68 (56-78)	73 (63–81)	69 (63 -75)
Best Overall response Complete remission Partial remission Stable disease Progressive disease Unable to determine	 29 37 24 11 0	 13 55 21 8 4	 12 61 15 10 2	 16 53 19 9 2
Secondary and Exploratory Outcomes				
DOR[c] as assessed by IRRC, months median (95% CI)	20 (13–20)	16 (8-20)	15 (9-17)	17 (13-20)
PFS[d] as assessed by IRRC, months median (95% CI)	18 (11, 22)	15 (11, 20)	12 (11, 18)	NA
OS[e], months[e] median (95% CI)	NR	NR	NR (19, NR)	NR
Abbreviations: CI – confidence interval; **NA** – not available; **NR** – not reached; **PFS** – progression-free survival; **OS** – overall survival; **BIRC** – Blinded Independent Review Committee; **CRR -** complete response rate**; DOR -** duration of response				
Notes:				

[a] ORR was defined as the percentage of treated patients with a best overall response of complete or partial remission, as per the revised IWG criteria for Malignant Lymphoma (2007 criteria).
[b] December-2016 database lock
[c] DOR was defined as the time from first response (CR or PR) to the date of the first documented tumour progression as determined by the investigator using the 2007 IWG criteria or death due to any cause, whichever occurred first. Database
[d] PFS was defined as the time from the first dosing date to the date of the first documented tumor progression (or death due to any cause, whichever occurred first
[e] OS was defined as the time from first dosing date to the date of death. For patients without documentation of death, OS was censored on the last date the subject was known to have been alive.

Source: [Younes, Lancet Oncol 2016; 17(9):1283-94][1], [Fanale, ICML 2017][2]

Limitations

- CHECKMATE-205 is a non-comparative open-label study with no active treatment or placebo control groups. Randomized comparisons between the study treatment (nivolumab) and its potential comparators are needed to justify the observed clinical efficacy and safety outcomes. Although nivolumab resulted in clinical and survival benefits, no conclusions could be made regarding the efficacy of this drug relative to currently used treatment options for patients with refractory cHL.
- The open label nature of the trials might introduce the risk of reporting and performance biases, as the study participants and the investigators were aware of the treatment assignments. This could particularly be important in reporting of subjective outcomes (e.g., AEs) by the patients and care providers.
- The trial is ongoing (not recruiting) and, therefore, the duration of follow up for a proportion of patients might not be long enough to make an inference on the observed survival benefits.
- In CHAECKMATE-205, ORR was the primary endpoint. PFS, OS, and health-related QoL endpoints were exploratory outcomes. Therefore the trial might not have been sufficiently powered to reliably estimate survival rates or quality of life outcomes.

CHECKMATE-039[6,7]

CheckMate039 was a Phase 1, open-label, multicenter, dose-escalation, and multi-dose study to assess the tolerability of nivolumab and the combination of nivolumab and daratumumab, with or without immunomodulatory drugs (pomalidomide and dexamethasone) in patients with relapsed and refractory hematological malignancies, including a cohort of 23 patients with Hodgkin lymphoma.

The trial included adult patients who had histologically confirmed evidence of relapsed or refractory Hodgkin lymphoma with at least one lesion measuring more than 1.5 cm, an ECOG performance-status score of 0 or 1, previous treatment with at least one chemotherapy regimen, and no autologous stem-cell transplantation (ASCT) within the previous 100 days. The expansion cohort (23 cHL patients) was treated at the maximum tolerated dose (3 mg/kg), determined during the dose escalation phase. A response assessment following administration of the first dose was obtained, and the treatment was administered every two weeks thereafter. Patients continued to receive study drug for up to two years or until confirmed CR, confirmed progressive disease or unacceptable toxicity. Patients who discontinued study treatment were followed for 100 days for safety data collection.

The primary objective of CHECKMATE-039 was to evaluate the safety and side-effect profile of nivolumab. Secondary objectives included characterizing the efficacy of nivolumab, based on best overall response (BOR), DOR, ORR, PFS, and OS, and assessing PD-1 ligand loci integrity and expression of the encoded ligands. The key safety and efficacy outcomes of CHECK<MATE-039 trial are presented in Table 1.2.

Efficacy

After a median follow-up of 86 weeks, ORR was reported in 20/23 (87%) of the patients; among those, 22% had a CR and 65% had a PR. However, the median DOR had not been reached. The investigator-assessed median time to response was 1.7 (range 0.7 to 8.9) months for all cHL patients, with time to CR being 5.3 (range 1.6 to 19.9) months, and time to PR 1.7 (range 0.7 to 8.9) months. The majority of responses occurred within the first 3 months (83.3% (15/18) total responders). Seven out of 18 responders (38.9%) had an ongoing response at the time of the data cut-off. [6]

The PFS rate at 24 weeks was 86% (95%CI: 62–95). The OS rates at 1 year and 1.5 year were 91% (95% CI 69.5 to 97.8) and 83 (95% CI 60.1 to 93.1), respectively. After a median follow-up of 86 weeks, the median PFS and OS had not been reached.[3]

Harms

At a median follow-up of 40 weeks, the incidence of drug- AEs of any grade that occurred in at least 5% of the patients was 78%. Grade 3 AEs were reported in 22% of patients. Overall, drug-related AEs were reported in 18 patients (78%). The most common AEs included rash (22%) and a decreased platelet count (17%). Drug-related grade 3 AEs were reported in 5 patients (22%), and included the myelodysplastic syndrome, pancreatitis, pneumonitis, stomatitis, colitis, gastrointestinal inflammation, thrombocytopenia, an increased lipase level, a decreased lymphocyte level, and leukopenia. No drug-related grade 4 or 5 adverse events were reported. No treatment-related deaths were reported. Twelve patients (52%) discontinued treatment; of those, two patients (9%) had toxic events (the myelodysplastic syndrome and thrombocytopenia).[6]

Table 1.2: Highlights of Key Efficacy Outcomes of CHECKMATE-039 trial

CHECKMATE-039 (n=23)		
Primary Outcome		
Safety Any AEs, n (%) Grade 3 AEs, n (%)	18 (78) 5 (22)	
Secondary and Exploratory Outcomes		
August 2015 database lock	By IRRC	By Investigator
ORR [a] %, (95% CI)	61 (39, 80)	87 (66, 97)[†]
Best Overall response Complete remission Partial remission Stable disease	 3 (13) 11 (48) 7 (30)	 5 (22) 15 (65) 3 (13)

CHECKMATE-039 (n=23)		
Time to Response[b]	1.2 (0.7-4.1)	1.7 (0.7-9.2)
DOR[c,] months median (95% CI)	NA (7.43, NA)	NA (15.5, NA)
PFS[d], months Median (95% CI)	Not reached	
PFS at 24 months[e]	NA	86% (62–95)
OS, months[e] median (95% CI)	Not reached	
Abbreviations: CI – confidence interval; **NA** – not available; **NR** – not reached; **PFS** – progression-free survival; **OS** – overall survival; **BIRC** – Blinded Independent Review Committee; **CRR -** complete response rate**; DOR -** duration of response		
Notes: † Primary outcome [a] ORR was defined as the total number of subjects whose best objective response was either a CR or PR divided by the total number of treated subjects. [b] Time to response was defined as the time from the date of the first dose to the date of the first response [c] DOR was defined as the time between the date of the first response and the date of first progression or the date of death. [d] PFS was defined as the time from the date of the first dose of study medication to the date of first disease progression or the date of death, whichever occurs first. [e] 16-Jun-2014 data cut-off date [f] OS was defined as the time between the date of first dose of study therapy and death. **Source**: [Ansell, NEJM 2015; 372(4):311-9][6], [EPAR, 2015][3]		

Limitations

- CHECKMATE-039 is a phase 1 open-label single arm study primarily designed to assess the safety and tolerability profile of nivolumab in the treatment of refractory hematologic malignancies, including cHL. Therefore, it is difficult to make a conclusion on the efficacy of nivolumab based on the data obtained from this study.
- The open label nature of the trials might introduce the risk of reporting and performance biases, as the study participants and the investigators were aware of the treatment assignments. This could particularly be important in reporting of subjective outcomes (e.g., AEs) by the patients and care providers.
- The trial is ongoing (not recruiting) and, therefore, the duration of follow up for a proportion of patients might not be long enough to make an inference on the observed survival benefits.

1.2.2 Additional Evidence

See Section 3, Section 4, and Section 5 for a complete summary of patient advocacy group input, Provincial Advisory Group (PAG) Input, and Registered Clinician Input, respectively.

Patient Advocacy Group Input

One patient advocacy group, Lymphoma Canada provided input on nivolumab for the treatment of patients with classical Hodgkin lymphoma (cHL).

From a patient's perspective, there are a number of symptoms associated with cHL that impact quality of life, which include fatigue or lack of energy, enlarged lymph nodes, drenching night sweats, itching, persistent cough and mental and emotional problems such

as anxiety and difficulties with concentrating. Respondents also reported on aspects of their life negatively impacted by cHL, including ability to work, personal image, family obligations, intimate relations, friendships and ability to attend school. Most respondents indicated that current treatment options (e.g. ABVD, GDP, BEACOPP and MOPP/COPP, radiation, stem cell transplant, BV and surgery) work well in managing their cHL symptoms. LC noted that toxicity associated with their previous treatments were of great concern to many respondents; specifically, fatigue, "chemo-brain", peripheral neuropathy, loss of menstrual periods, thyroid dysfunction, sterility and lung damage were the most commonly reported. LC also indicated that respondents also experienced one or more late or long-term treatment-related side effect (lasting longer than 2 years or appearing later than 2 years after the end of treatment). In the current sample LC noted that 93% of respondents had been treated with at least one line of conventional and 16% of respondents had received ≥ 3 lines of therapy. Respondents who have not experienced nivolumab expect that it demonstrates "effectiveness" (i.e., offer disease control and remission) followed by "minimal side effects" or "less side effects than current treatments". Respondents who have experience with nivolumab reported few side effects, and that they were tolerable. Some of the side effects reported with nivolumab included fatigue, muscle or joint pain, diarrhea, constipation, headache, shortness of breath, rash and back pain. The most common reason for choosing treatment with nivolumab was that there were no other treatment options available. At the time of the survey, LC reported that four respondents were no longer being treated with nivolumab (two had completed their full course of treatment; one respondent did not respond to the drug; and one respondent proceeded to allogeneic transplant after achieving a complete response with nivolumab). The majority responded that nivolumab had positively impacted their health and well-being, notably no negative impacts on school and family obligation had been experienced. Respondents also reported that nivolumab had positive impacts on their ability to work, attend school, travel, participate in activities, and on their personal relationships.

Provincial Advisory Group (PAG) Input

Input was obtained from all of the provinces participating in pCODR. The following were identified as factors that could impact the implementation:

Clinical factors:

- New treatment option for relapsed or refractory classical Hodgkin Lymphoma (cHL)
- Clarity on eligible patients

Economic factors:

- New treatment option
- Chair time

Registered Clinician Input

Two group clinician inputs were provided.

The clinicians providing input indicated that nivolumab would be an additional line of therapy for patients who have relapsed disease following stem cell transplant and Brentuximab vedotin (BV) and who have no other effective options. They noted that nivolumab offers patients hope of long term cure, given the high response rates and remissions. The magnitude of benefits allows

patients, who are typically 20 to 30 years old, to return to work and enjoy an excellent quality of life. The side effects are as expected for immunotherapies and are manageable by clinicians who are used to dealing with immune-related adverse events.

Summary of Supplemental Questions

Supplementary Question: Summary and critical appraisal of the Manufacturer-submitted indirect treatment comparison (ITC) of nivolumab to BV and best supportive care (BSC) in relapsed or refractory cHL after failure of ASCT1

The submitted ITC was conducted with the objective of conducting an indirect comparison of nivolumab against BV, and BSC in the management of patients with cHL who have failed ASCT.[8] Of note, the ITC analysis did not include all comparators relevant to the submitted funding request. The indirect analyses focused on the comparison of nivolumab versus BV and BSC (mix of chemotherapies) in patients who failed ASCT and were BV-naïve (Cohort A of CHECKMATE-205). The ITC analysis did not include a comparison between nivolumab and a potential comparator (e.g. chemotherapy regimens or pembrolizumab) in patients who have failed both ASCT and subsequent BV treatment (cohort B) or in those who have had ASCT and BV in any treatment order (BV before and/or after ASCT) (cohort C).

The Manufacturer performed naïve indirect treatment comparisons (with no adjustment for prognostic factors or effect-modifiers), supplemented with matched adjusted indirect comparisons (MAICs), which allowed for matching baseline characteristics of the study populations, and comparing individual patient level data from one trial with aggregate data from other studies. The MAIC used data from CHECKMATE-205 Cohort A (BV-naïve) to perform indirect comparison of nivolumab against BV, and BSC.

Due to the short follow up in the included nivolumab study (CHECKMATE-205), different scenarios were considered to quantify uncertainty around the expected PFS and OS benefits, over a 15-year time horizon, for nivolumab. Under the most conservative scenarios, in patients who received nivolumab the expected PFS was 5.4 months shorter, and the expected OS was 33.6 months longer than those of patients receiving BV. However, the incremental PFS and OS benefits of nivolumab over BV did not reach statistical significance. Nivolumab OS was estimated to be between 59.2 months longer than that of patients receiving BSC.

Limitations

The results of the submitted ITC should be interpreted with caution due to the limitations that arise from the lack of comparative evidence, insufficient follow-up data for nivolumab studies, lack of quality appraisal for the included studies, lack of indirect comparisons for safety and QoL data, and the use of naïve and model-based indirect comparisons. Therefore, the relative efficacy of nivolumab over BV or BSC remains uncertain in cHL patients who failed on ASCT and were BV-naïve.

Furthermore, because the submitted ITC did not include cHL patients who failed on both ASCT and BV, no conclusions can be made on the relative efficacy of nivolumab compared to its potential comparators (e.g., pembrolizumab and BSC) in this patient population

See section 7.1 for more information.

Comparison with Other Literature

The pCODR Clinical Guidance Panel and the pCODR Methods Team did not identify other relevant literature providing supporting information for this review.

1.2.3 Factors Related to Generalizability of the Evidence

Table 2 addresses the generalizability of the evidence and an assessment of the limitations and sources of bias can be found in Sections 6.3.2.1a and 6.3.2.1b (regarding internal validity).

Table 2: Assessment of generalizability of evidence for nivolumab for cHL

<table>
<tr><th>Domain</th><th>Factor</th><th>Evidence</th><th>Generalizability Question</th><th>CGP Assessment of Generalizability</th></tr>
<tr><td rowspan="2">Population</td><td>Performance status</td><td>The included trials limited eligibility to patients with an ECOG performance status of 0 or 1.

<u>CHECKMATE-205</u>
<table><tr><td>ECOG</td><td colspan="3">Study Cohorts</td></tr><tr><td></td><td>A</td><td>B</td><td>C</td></tr><tr><td>0</td><td>40 (63.5%)</td><td>42 (52.5%)</td><td>49 (50.5%)</td></tr><tr><td>1</td><td>23 (38%)</td><td>38 (48%)</td><td>50 (50%)</td></tr></table>
<u>CHECKMATE-039</u>
ECOG 0: n=11 (47.8%)
ECOG 1: n=12 (52.2%)</td><td>Does performance status limit the interpretation of the trial results (efficacy or toxicity) with respect to the target population (e.g., Canadian clinical practice, patients without the factor, etc.)?</td><td>Results can be generalized to the population of patients with ECOG performance status of 0-3, as the treatment is fairly non-toxic, and patients often experience rapid improvement of symptoms (B symptoms, asthenia, pruritic, fatigue) within 1-2 cycles.</td></tr>
<tr><td>Line of therapy</td><td>The trials assessed 3rd+ lines of therapy:

<u>CHECKMATE-205</u>
CHECKMATE-205 eligibility criteria required that patients have recurrent cHL after failure of ASCT
Patients were BV-naïve in Cohort A, failed on ASCT and subsequent BV (Cohort B), or had previous treatment with ASCT and BV in any order (Cohort C). The trial did not include ASCT-naïve patients.</td><td>Are the results of the trial generalizable to other lines of therapy?</td><td>The results from cohorts A and B of the CHECKMATE-205 trial, could be generalized to those patients with relapsed or progressed cHL who are: (1) ASCT ineligible and BV naïve, or
(2) ASCT ineligible and have received BV. This latter subgroup has recently received a positive pERC recommendation for pembrolizumab. Given the similar PD1-I “class-effect” for pembrolizumab and nivolumab, it seems likely that patients who do well on one of the two agents would do equally well on the other.</td></tr>
<tr><td>Intervention</td><td>Dose and Schedule</td><td><u>CHECKMATE-205</u>
Nivolumab 3 mg/kg IV infusion, over 60 minutes, on the first day of each 14-day cycle

<u>CHECKMATE-039</u>
3 mg/kg at week 1, 4 (dose escalation), and every 2 weeks thereafter</td><td>If the dose and/or schedule is not standard, are the results of the trial relevant in the Canadian setting?</td><td>Nivolumab as given in the trials at 3 mg/kg IV infusion every 2 weeks reflects standard dose and schedule as used in Canada.</td></tr>
</table>

Domain	Factor	Evidence	Generalizability Question	CGP Assessment of Generalizability
	Treatment Intent	Palliative treatment intent.	Are the results of the treatment generalizable to an alternative treatment intent? (i.e., if the trial is palliative in intent, could the therapy also be used in the adjuvant setting or vice versa?)	Use of treatments for relapse post-ASCT are generally with palliative intent. Nivolumab has a very high activity in cHL and at this stage it is not known if it may be curative for some patients. There is currently no evidence for the use of Nivolumab with curative treatment intent in the pre-ASCT setting or for use of consolation treatment post-ASCT.
	Number of treatment cycles	**CHECKMATE-205** Patients in Cohorts A, B, and C were treated with nivolumab 3 mg/kg, intravenously, every 2 weeks until unacceptable toxicity or progressive disease according to the International Working Group criteria for Malignant Lymphoma (2007 IWG) criteria.	Are the number of treatment cycles allowed in the trial applicable in the Canadian setting?	Giving nivolumab at the dose used in the CHECKMATE-205 trial until unacceptable toxicity or disease progression is acceptable in Canadian practice.
Comparator	Standard of Care	**CHECKMATE-205** Single-arm, multi-cohort, nonrandomized trial **CHECKMATE-039** Single-arm, nonrandomized trial	If the comparator is non-standard, are the results of the trial applicable in the Canadian setting?	CHECKMATE-205 and CHECKMATE-039 are single arm studies and do not have any comparators. In the Canadian context either single agent or combination therapy may be used following progression after ASCT and BV (including involved field or extended field radiation).The results from these two non-comparative phase I and II studies compare favorable to currently available therapies, such as single agent vinca alkaloids or gemcitabine. BV therapy is currently funded for patients who fail ASCT. Due to lack of robust comparative evidence between BV and nivolumab it is impossible to

Domain	Factor	Evidence	Generalizability Question	CGP Assessment of Generalizability
				conclude if one drug is superior to the other.
Outcomes	Appropriateness of primary and Secondary Outcomes	**CHECKMATE-205** Primary: ORR by IRRC Secondary: ORR by investigator, DOR by IRRC and investigator, CR and PR by IRRC Exploratory: PFS by IRRC and investigator, OS, Safety, HRQoL **CHECKMATE-039** Primary: Safety, ORR by investigator Secondary: ORR by IRRC, time to response, DOR, PFS Exploratory: OS, immunogenicity	Were the primary and secondary outcomes appropriate for the trial design?	ORR is a meaningful outcome in this setting. An 80% ORR is unprecedented for relapsed cHL that has failed all other available options, Despite the lack of randomized comparators this is clearly a superior treatment to the current standard of conventional chemotherapy.
Setting	Location of the participating centres	**CHECKMATE-205** 89% of the participating sites were located in academic centers and 11% were located in community hospitals [checkpoint 20-N0v-2017]. **CHECKMATE-039** 71% of the participating sites were located in academic centers and 29% were located in community hospitals [checkpoint 20-N0v-2017].	If the trial was conducted only in academic centres are the results applicable in the community setting?	Results would be generalizable to community practice settings, as nivolumab is used routinely and successfully in community practice to treat other cancers.
	Supportive medications, procedures, or care	In both of the included trials, corticosteroids were permitted, in topical, ocular, intra-articular, intranasal, and inhalational forms, and for the purposes of prophylaxis or treatment of AEs or non-autoimmune conditions.	Are the supportive medications, procedures, or care used with the intervention in the trial the same as those used in Canadian clinical practice?	Supportive therapies used in this trial are the same as those used in Canadian clinical practice.

Abbreviations: ASCT – autologous stem cell transplant; **BSC** – best supportive care; **BV** – brentuximab vedotin; c**HL** – classical Hodgkin Lymphoma**; CT** scan - Computerized Tomography scan; DOR – duration of response; **ECOG** - Eastern Cooperative Oncology Group; HRQoL – Health related quality of life; **IRRC** - Independent radiologic review committee; ORR – objective response rate; **OS** – overall survival; **PET** scan - Positron Emission Tomography; **PFS** – progression free survival.

1.2.4 Interpretation

Burden of Illness and Need

According to 2017 Canadian Cancer Statistics, Classical Hodgkin Lymphoma represents approximately 0.5% of all new cancers diagnosed annually, 0.2% of cancer deaths, and totals approximately 1000 new cases and 140 deaths each year in Canada.[9] Initial chemotherapy ± radiotherapy cures approximately 75% of cHL patients, and intensive salvage therapy with autologous hematopoietic stem cell transplant (ASCT) cures approximately half of relapsed patients.[10] Patients who are not candidates for ASCT, or who relapse after ASCT have a particularly poor prognosis, with a median survival of only 2 years when receiving conventional

palliative chemotherapy agents.[11] In Canada, most patients who relapse after ASCT are currently treated with Brentuximab vedotin (BV), to which approximately 75% of patients respond and 1/3 achieve a complete response.[12] Although the median PFS following BV is only 6 months, approximately ~20% of patients (~half of CR patients) enjoy prolonged PFS beyond 5 years.[13] Unfortunately, provinces generally do not fund BV for patients who have not had a prior ASCT, based upon a prior pCODR recommendation for the use of BV. Those patients who relapse after BV have <50% chance of response and median PFS of only 3-4 months following further palliative chemotherapy.[14] Therefore, patients who relapse after BV, or who are not candidates for ASCT, or for BV, represent 3 groups of patients with unmet need, who have no effective treatment options and who will die from their cHL. These 3 groups of unmet need patients total only approximately 100 patients/year in Canada. The majority of these patients are fairly young in age, and could return to work if their cancer was put into remission with non-toxic therapy.

The CGP agrees with clinicians who provided input for this submission that Nivolumab would address this unmet need for patients who relapse after ASCT and after BV, as well as those patient who are not candidates for ASCT, and for those patients who are not candidates for BV due to severe neuropathy, or lack of access and funding. There is no biological rationale to assume that outcomes of PD1-inhibitor therapy using Nivolumab would be any less effective or significantly more toxic for cHL patients who have never undergone ASCT relative to those who have received ASCT. There is extensive evidence on the effectiveness and safety of PD1-inhibitor therapy for large numbers of cancer patients who have never received ASCT such as melanoma and lung cancer,[15] as well as for Pembrolizumab (another PD1-inhibitor) for relapsed cHL without prior ASCT,[16] and this evidence does not suggest higher toxicity for these patients relative to the post-ASCT population of relapsed cHL. The safety and efficacy results of Pembrolizumab and Nivolumab for multiply relapsed cHL appear very similar, and this strongly suggests that the class effect of PD1-inhibition is a useful strategy to manage cHL that has relapsed after other treatments.[17] Likely, the availability of both these agents will result in cost-savings for the Canadian healthcare system over time, as compared to having only one such agent available.

Effectiveness

The pCODR systematic review included two nonrandomized trials, the phase 2 CHECKMATE-205 (N = 243) and the phase 1 CHECKMATE-039 (N=23). CHECKMATE-039 was primarily designed to assess the safety and tolerability profile of nivolumab in the treatment of refractory hematologic malignancies, including cHL. Therefore, it is difficult to make a conclusion on the efficacy of nivolumab based on the data obtained from this study. However, investigator-assessed ORR for cHL in the CHECKMATE-039 trial was 87% (95% CI: 66–97%) with a CR rate of 17%, and PFS at 24 weeks of 86% (95%CI: 62–95).

CHECKMATE-205 (n=243, median age 34 years (18 to 72), was a non-comparative, multi-cohort, single-arm, open-label, phase 2 study of nivolumab 3 mg/kg intravenous (IV) on the first day of each 14-day cycle, administered until unacceptable toxicity or disease progression, in patients with relapsed cHL. The study cohorts included patients who:

- had failed on ASCT and were BV-naïve (Cohort A, n=63);
- had relapsed or failed on prior BV treatment as a salvage therapy after failure of ASCT (Cohort B, n=80); or
- had prior ASCT and BV in any treatment order (i.e. BV before and/or after ASCT) (Cohort C, n=100). Of the 100 patients in cohort C, 33 received BV before, 58 after, and 9 both before and after ASCT.

Despite heavy pre-treatment with a median of four prior systemic cancer regimens (range; 2-15), and 67.1% prior radiotherapy, the ORR was achieved in 65% of patients in Cohort A, 68% of patients in Cohort B, and 73% of patients in Cohort C, with corresponding complete remission rates of 29%, 13%, and

12%, respectively. The median duration of IRRC-assessed objective response reached 20 months (95% CI 13 – 20) in Cohort A, 16 months (95% CI 8 – 20) in Cohort B, and 15 months (95% CI 9 – 17) in Cohort C, and PFS rates were 18.0 months (95% CI 11 - 22) in cohort A, 15 months (95% CI 11 - 20) in cohort B, and 12 months (95% CI 11 - 18) in Cohort C. After a median follow-up 19.12 months the OS rate was 93.4% in Cohort A; after a median follow-up 22.70 months the OS rate was 89.2% in Cohort B; and after a median follow-up 16.16 months the OS rate was 88.7% in Cohort C. Quality of life assessment in Cohort B (58% of patients) revealed least squares mean score change from baseline at week 33 of 19.1 (±3.1) for EQ-5D VAS and 7.6 (±2.3) for the EORTC QLQ-C30 global health/quality of life status scale. When the data were pooled for Cohorts A, B, and C, nivolumab treatment resulted in clinically meaningful and statistically significant improvement in general and cancer-specific patient related outcomes (fatigue, dyspnea, appetite loss, physical functioning, role functioning). Improvement started early (Week 9) and persisted to Week 93.

Although there are several limitations to the data supporting nivolumab for relapsed cHL patients, the CPG agrees that nivolumab will achieve meaningful benefit for these patients. One limitation is that CHECKMATE-205 is a non-comparative open-label study. However, it is unclear what palliative therapy would be considered by patients and ethics board to be a reasonable comparator to nivolumab in a prospective phase III trial. Equipoise between nivolumab and a palliative chemotherapy agent does not exist. Another limitation of CHECKMATE-205 is that the open label nature of the trial might introduce the risk of reporting and performance biases, however, it is the experience of clinicians that well-tolerated treatments that result in high response rate >50% and significant complete remission rates for widely disseminated cancers generally also result in meaningful clinical improvements in symptoms and quality of life. The results reported in the phase 2 study of nivolumab meet these benchmarks for response and quality of life. Finally, in CHECKMATE-205, ORR was the primary endpoint. PFS, OS, and health-related QoL endpoints were exploratory outcomes. The trial might not have been sufficiently powered to reliably estimate survival rates or quality of life outcomes. Nevertheless, the reported outcomes definitely suggest improvements in these outcomes relative to those expected with palliative chemotherapy alone.

It is difficult to compare the results of CHECKMATE-205 cohort A (BV naïve) to those of the pivotal phase II BV study (ORR 75%, CR 34%, 5yr PFS 22%, 5yr OS 41%),[4-5] because of differences in patient characteristics (e.g., all patients in the BV trial had prior ASCT with median time from ASCT to relapse of 6.7 months, and median number prior regimens of 3.5 [1-13], 71% primary refractory disease, time from diagnosis to BV 40 months) and trial outcome assessments. The CGP agreed that indirect treatment comparisons are inherently subject to bias, especially in light of insufficient follow-up data for nivolumab, baseline differences in patient and disease characteristics (especially treatment effect modifiers), differences in trial designs, inability to control for unknown confounders, and lack of direct comparative evidence. Because of this, it is impossible to conclude if nivolumab is superior to BV. Ongoing phase III trials will compare BV to Pembrolizumab, as well as BV to BV + nivolumab. The results of CHECKMATE-205, however, strongly suggest that nivolumab is a very reasonable treatment option for those patients who are not appropriate candidates to receive BV due to severe peripheral neuropathy or lack of funding for BV therapy.

Further there is insufficient evidence to support the assumption that the treatment effect of nivolumab is the same in all three subgroups of cohort C. Therefore, the CGP was unable to determine the magnitude of treatment effect in individual subgroups of cohort C, such as patients who received BV before ASCT.

The dose for nivolumab is 3 mg/kg administered intravenously over 60 minutes every 2 weeks until progression or unacceptable toxicity. The CGP confirmed that while flat dosing is widely used in solid tumours, there is currently insufficient evidence available to recommend using cost saving dosing strategies of 3mg/kg up to a dose cap of 240mg every two weeks and 6mg/kg up to a dose cap of 480mg every four weeks.

This was stated in reference to input from PAG which was seeking clarity on the above mentioned dosing strategies.

Safety

The most common drug-related AEs in 243 nivolumab-treated patients (CHECKMATE-205 Cohorts A, B, and C) included fatigue (23%), diarrhea (15%), and infusion reactions (14%). The most common drug-related serious AEs were infusion reactions (2%) and pneumonitis (1%). Serious AEs included fatigue (1%), diarrhea (1%), rash (1%), infusion reactions (<1%), and autoimmune hepatitis (1%). The most common drug-related AEs which led to discontinuation of the study treatment were pneumonitis (2%) and autoimmune hepatitis (1%). In general, these side effects are as expected for PD1 inhibitors with less than 5% having grade 3/4 adverse events and are manageable by clinicians who are used to dealing with immune-related adverse events.

1.3 Conclusions

Patients who failed ASCT and are BV-naïve; Cohort A

The Clinical Guidance Panel concluded that there ***is not*** an overall net clinical benefit to nivolumab compared with BV, with relapsed or progressed cHL after 3 or more lines of systemic therapy including ASCT. This conclusion is based on the results achieved in cohort A (n = 63) of the non-comparative CHECKMATE-205 study. While the CGP was confident that nivolumab produces a tumor response (ORR = 65%) in this patient group, the CGP was unable to determine the magnitude of effect compared with BV given the lack of comparative data and long-term outcomes important to patients, such as OS, PFS, ORR and QoL. The CGP acknowledge that nivolumab showed a manageable toxicity profile but was unable to determine how it compares with the safety profile of BV treatment, which is generally mild and manageable. Further, given the availability of BV treatment in this patients group, the CGP was uncertain if nivolumab addressed an unmet need. The CGP agreed that more robust direct evidence from a randomized trial is required to address the comparative effectiveness and safety of nivolumab compared to BV in this setting. Indirect treatment comparisons are inherently subject to bias, especially due to lack of comparative evidence in this setting and insufficient follow-up data for nivolumab.

However, the CGP agreed that the results of cohort A strongly suggest that nivolumab is a very reasonable treatment option for those patients who have relapsed after ASCT and are not appropriate candidates to receive BV due to severe peripheral neuropathy.

Patients who have relapsed or failed on both ASCT and subsequent BV treatment; Cohort B

The Clinical Guidance Panel concluded that there ***is*** an overall net clinical benefit to nivolumab compared with chemotherapy, with relapsed or progressed cHL after both ASCT and subsequent BV treatment. This conclusion is based on the results achieved in cohort B (n = 80) of the non-comparative CHECKMATE-205 study that demonstrated a clear statistically significant and clinically meaningful overall response rate (68%) with prolonged durability of responses and encouraging early PFS. The toxicity profile was better than that seen with chemotherapy, with a low rate of immune-related adverse events and there was evidence of improvement in quality of life over the course of the CHECKMATE-205 trial. These data suggest much greater clinical benefit than what would be expected from standard chemotherapy regimens in this setting. The CGP agreed that there is a high unmet need for more effective treatment options in this heavily pre-treated patient population and that conducting a randomized controlled trial in this setting would likely not be feasible. Responses in this patient population are important because of accompanying improvement in distressing symptoms (pruritis, fever, night sweats) and improvement in performance status.

Patients who had ASCT and BV in any treatment order; Cohort C

The Clinical Guidance Panel concluded that there **may be** an overall net clinical benefit to nivolumab compared with chemotherapy, with relapsed or progressed cHL after ASCT and BV in any treatment order. This conclusion is based on the results achieved in cohort C (n = 100) of the non-comparative CHECKMATE-205 study that demonstrated a clear statistically significant and clinically meaningful overall response rate (73%) with prolonged durability of responses and encouraging early PFS. The toxicity profile was better than that seen with chemotherapy, with a low rate of immune-related adverse events and there was evidence of improvement in quality of life over the course of the CHECKMATE-205 trial. These data suggest much greater clinical benefit than what would be expected from standard chemotherapy regimens in this setting. However, the CGP acknowledged that there is insufficient evidence to support the assumption that the treatment effect of nivolumab is the same in all three subgroups of cohort C. Therefore, the CGP was unable to determine the magnitude of treatment effect in individual subgroups of cohort C, such as patients who received BV before ASCT. Further the CGP was uncertain if nivolumab addressed an unmet need in patients in cohort C, as treatment options may vary across the different patient subgroups within cohort C. For example, patients who responded to BV + salvage chemotherapy and then an ASCT may be retreated with BV; however, patients who failed on both ASCT and subsequent BV will be treated with palliative chemotherapy.

In making these conclusions, the Clinical Guidance Panel also considered that:

- Brentuximab vedotin is currently standard therapy in Canada for patients who have relapsed after ASCT, but is not available in many provinces to those who have not received ASCT. The CGP strongly suggested that the results from cohorts A and B of the CHECKMATE-205 trial, could be generalized to those patients with relapsed or progressed cHL who are: (1) ASCT ineligible and BV naïve, or (2) ASCT ineligible and have received BV. The former group has a high unmet need for effective treatment options due the unavailability of BV for this patient population in most provinces. There is no biological rationale to assume that outcomes of nivolumab therapy would be any different in patients who have never undergone ASCT relative to those who have received ASCT. The letter subgroup (ASCT ineligible patients who have received BV) has recently received a positive pERC recommendation for pembrolizumab. Given the similar PD1-I "class-effect" for pembrolizumab and nivolumab, it seems likely that patients who do well on one of the two agents would do equally well on the other.

- The proportion of patients in cohort C who received BV before (33%), after (58%) and both before and after ASCT (9%) are not representative of patients in Canadian practice. The CGP estimates that in Canada the majority of patients (approximately 95%) will receive BV after ASCT. Receiving treatment with BV before transplant is very uncommon, but could have occurred as part of a clinical trial. Very rarely, some patients may have accessed BV pre-ASCT by paying for it themselves, or through a special access program. Further there is insufficient evidence to support the assumption that the treatment effect of nivolumab is the same in all three subgroups of cohort C. Therefore, the CGP was unable to determine the magnitude of treatment effect in individual subgroups of cohort C, such as patients who received BV before ASCT. Further the CGP was uncertain if nivolumab addressed an unmet need in patients in cohort C, as treatment options may vary across the different patient subgroups within cohort C. While patients who have failed ASCT and subsequent BV do not have the option of further BV, patients who responded to BV + salvage chemotherapy and then an ASCT could be retreated with BV.

- BV is not currently funded in Canada for consolidation therapy post-ASCT for patients at increased risk of relapse, but may be in the near future; this would decrease the number of patients who would receive nivolumab after BV for relapse following ASCT.

- The data supporting this conclusion are from non-randomized studies. Indirect treatment comparison are inherently subject to bias and make these comparisons difficult to interpret. Hence there is no reliable estimate of the comparative efficacy or effectiveness of nivolumab to chemotherapy or BV. However, since equipoise between nivolumab and a palliative chemotherapy agent does not exist it is unlikely that a randomized controlled trial would be conducted in the setting of relapsed or progressed cHL after ASCT and subsequent BV (cohort B). On the other hand results from ongoing phase III trials comparing BV to Pembrolizumab, as well as BV to BV + Nivolumab may provide important information on relative PFS, toxicity and quality of life data between BV and PD-1 inhibitors in the setting of relapsed or progressed cHL after 3 or more lines of systemic therapy including ASCT (cohort A).

- The follow-up of both trials considered is short and additional data on longer-term PFS and OS outcomes as well as toxicities are awaited.

- Given the lack of direct comparison between pembrolizumab and nivolumab for cHL patients who have relapsed after ASCT and after BV and given the similar PD1-I "class-effect" for these two agents, it seems likely that the choice between pembrolizumab and nivolumab in this setting will mostly depend upon relative overall cost as well as the frequency and duration of administration (impacting systemic infusion clinic capacity). The CGP agreed that there is not a clear efficacy or toxicity argument to choose one over the other.

2 BACKGROUND CLINICAL INFORMATION

This section was prepared by the pCODR Lymphoma Clinical Guidance Panel. It is not based on a systematic review of the relevant literature.

2.1 Description of the Condition

Classical Hodgkin lymphoma (cHL) is an uncommon but distinct lymphoma subtype that typically presents in young adults, but is seen in both children and adolescents, and those over the age of 60 years.[9] cHL accounts for approximately 8-10% of all diagnoses of lymphoma. cHL is characterized by rare malignant Reed-Sternberg cells, which are positive for CD30 and negative for the B cell antigens CD20 and CD79a; this includes nodular sclerosis, mixed cellularity and CHL not otherwise specified subtypes. PDL-1 is strongly expressed by cHL R-S cells and by infiltrating cells of the microenvironment, but is less strongly expressed on the malignant cell population of nodular lymphocyte predominant Hodgkin Lymphoma (NLPHL)[18]; this latter subgroup comprises only about 5% of all patients with Hodgkin Lymphoma (HL). The median age at diagnosis in most reported series is 35-40 years and approximately 15% are older than 60 years. There are approximately 900 new cases of Hodgkin lymphoma in Canada each year and approximately 160 Canadians will die annually from this disease. [9]

2.2 Accepted Clinical Practice

Approximately two thirds of patients with HL will present with localized disease (stage I and II according to the Ann Arbor classification), and are generally treated with combination chemotherapy and involved field radiation (IFRT). [19] Those who present with advanced stage disease (stage III and IV) and some with stage I and II who present with constitutional ("B") symptoms or for whom radiation is felt to carry significant risk of late toxicities (second cancers, cardiovascular disease) are usually managed with combination chemotherapy alone.[19] In Canada, the standard regimen is ABVD (doxorubicin, bleomycin, vinblastine and dacarbazine) for stage I-II disease (2-4 cycles prior to IFRT depending on risk factors) and for advanced stage disease (6 or 8 cycles). Increasingly, fluorodeoxyglucose (FDG)-positron emission tomography (PET) scanning is being used to direct treatment decisions in those with early and advanced HL, with the goal of limiting toxicities in those with favourable response following 2 cycles of therapy, and improving outcome through treatment intensification for those with less than complete response. [20] Despite the excellent complete remission rates with current doxorubicin, vinblastine, bleomycin, dacarbazine (ABVD) chemotherapy (>95% for localized and >80% for advanced stage disease), relapse is experienced by up to 10-15% of patients with early and 30% of those with advanced disease.[10,21]

Patients who experience treatment failure (disease progression on or relapse after primary therapy) are usually candidates for second-line (sometimes called salvage) chemotherapy followed by high-dose chemotherapy supported by autologous stem cell transplantation (ASCT). [10,22] The outcomes of this second treatment are most favourable in those with first remission duration longer than one year, lower disease burden at relapse and a complete response to second line chemotherapy assessed by either computed tomography (CT) scan or FDG-PET scanning. Approximately 50% of those undergoing ASCT will be alive and relapse-free five years after treatment and are generally considered cured. ASCT is not considered appropriate treatment for older patients (those older than 70 years), especially those with significant medical comorbidities. The results of ASCT are poor in patients with HL that is refractory to initial therapy (progression during or within 3 months of completion of treatment), those with less than a complete response to salvage therapy or those who require more than one second-line regimen prior to ASCT. [22] For those who experience disease progression following ASCT, the prospects of long term remission

with additional therapy are very limited, and the duration of disease control (as measured by progression free survival) is very short with currently available therapies. The median survival following relapse after ASCT is approximately 2-3 years, and is shorter for patients who relapse within 6 months of transplant and for those transplanted with disease that was refractory to primary therapy.[11]

Treatment of patients with relapse after ASCT has generally been for relief of symptoms and employs single agent chemotherapy. The most common drugs used are vinblastine, gemcitabine or vinorelbine, which are given every other week (vinblastine) or weekly intravenously for 3 weeks out of 4 each month, unless hematologic toxicity mandates a shorter cycle of 2 doses every 3 weeks (vinorelbine, gemcitabine). [23-25] Reported response rates range from 20-40% and progression-free survival from 6-8 months. Combination regimens, such as, gemcitabine, vinorelbine and liposomal doxorubicin (GVD) may achieve response rates that appear higher than with the single agents above, but progression-free survival is similar and hematologic toxicity of this combination therapy is significant. [26] Due to restrictions on reimbursement in many provinces, this regimen is not generally available in Canada, and other combination regimens such as COPP (cyclophosphamide, vincristine, procarbazine, prednisone) are used if patients have good performance status and bone marrow reserve. Involved field radiation is beneficial for those with localized relapse outside of a previous radiation field, but there are few long-term survivors.

In some centres, for young patients who have relapsed after ASCT with a long disease-free interval (more than one year), and a good response to additional salvage therapy, reduced intensity allogeneic stem cell transplantation from an HLA-matched sibling donor or unrelated matched donor, or haploidentical donor, may be considered. Overall, allogeneic transplantation may be considered appropriate therapy for approximately 10-15% of patients who relapse after ASCT. [27-30] Otherwise, treatment following relapse after ASCT is generally symptomatic and considered palliative.

The anti-CD30 chemoimmunoconjugate brentuximab vedotin (BV) is approved for the treatment of patients with HL after failure of ASCT or at least two prior multi-agent chemotherapy regimens. [31] In a large phase II trial in heavily pretreated patients (median number of prior regimens 3.5, range 1-11), the response rate to BV at a dose of 1.8 mg/kg every 3 weeks was 75% and complete response rate 34%; median progression-free survival was 6 months and median duration of complete response 20.5 months. [12,32] In most provinces, BV has become the treatment of choice as initial therapy for relapse after ASCT because of its favourable toxicity profile (grade 3 neutropenia: 14%, grade 4: 6%; other grade 3-4 events, < 2%). Direct comparison to other agents has not been carried out, but in a correlated survival analysis of a subgroup of patients who had received systemic therapy for relapse following ASCT and before treatment with BV, PFS was significantly longer with brentuximab compared to the prior systemic treatment (7.8 vs 4.1 months, p<.001). [12]Funding for BV for those who are not candidates for ASCT because of age, comorbidities or refractoriness to salvage therapy is not uniform across Canada and results in a significant treatment gap for this subgroup of patients in most provinces.

In a trial reported by Moskowitz et al, 329 patients with HL refractory to primary therapy, relapse within one year of completion of therapy or extranodal involvement at relapse (i.e. high risk for treatment failure) were randomized following ASCT to brentuximab (1.8mg/kg IV every 3 weeks for 16 doses) or placebo infusion as maintenance treatment. [33] These risk factors for treatment failure are present in approximately 50% of patients who undergo ASCT in Canada, although the exact proportion may vary according to the referral practice of the transplant centre. This study showed a significant improvement in median progression-free survival with BV compared to placebo (43 vs 24 months, HR 0.57 [0.40-0.81]), regardless of the number of risk factors present at the time of initiation of salvage chemotherapy. No difference in overall survival has been reported to date. This trial has led to the approval of BV as maintenance therapy post-ASCT in the US and

many countries in Europe, and currently this treatment is available in British Columbia as a treatment standard. It may be anticipated that an increasing number of patients who relapse after ASCT in Canada will have had BV as part of their second attempt at cure, creating a need for new therapies in this population. In addition, current trials are evaluating the impact of the addition of BV to primary therapy in patients with advanced stage HL, and as a component of induction therapy prior to transplant, either in combination or in the setting of poor response to standard platinum-based salvage treatment. Thus, the number of patients with relapsed and refractory HL who require additional therapy and who do not have access to BV, or who would not be expected to benefit from re-treatment with BV because of toxicity or short remission, is expected to increase, and new therapies for this population are clearly needed.

2.3 Evidence-Based Considerations for a Funding Population

There are a variety of mechanisms by with the malignant Hodgkin-Reid Sternberg (RS) cells in cHL evade the immune system and persist despite therapy, including secretion of cytokines that attract regulatory T cells and inhibit cytotoxic T cells; overexpression of FAS ligand leading to apoptosis of CTLs, and increased expression of the programmed death receptor (PD1) ligands PDL-1 and PDL-2. [34] RS cells demonstrate copy number gain or amplification of chromosome 9p24.1, the region that includes genes for PD-L1, PD-L2 and for JAK2, resulting in constitutive activation of the JAK-STAT pathway, which also leads to PDL overexpression. [35] PD-L1 expression on the surface of Hodgkin Reid Sternberg cells has been shown to be correlated with these genetic alterations, leading to engagement of the PD-1 receptor on T cells and induce PD-1 signaling and T-cell exhaustion by reversible inhibition of T-cell activation and proliferation.

The novel PD-1 antibodies nivolumab and pembrolizumab have been tested in patients with relapsed cHL, producing high response rates and resulting in relatively little toxicity. Among 80 patients with refractory cHL treated with nivolumab 3mg/kg IV every 2 weeks, the overall response rate was 66% (CR rate 9%) and 6 month PFS was 76%; in patients progressing after ASCT and then BV. According to an extended follow-up (of about 1 year) for this phase 2 trial by Younes at al. (2016) the response rates were similar in patients who progressed after ASCT and who had not received prior BV (ORR 65%, CR 29%) and in those who failed ASCT and had received treatment with BV at any time point (before and/or after ASCT) (ORR 73%, CR 12%); median PFS in the former and latter cohorts was 18 and 12 months, respectively. [1]

Treatment with pembrolizumab 200 mg IV every 3 weeks resulted in an overall response rate of 74% (CR 21%) in patients progressing after ASCT and then BV [16]; response rates in patients who progressed on salvage therapy and on BV, without prior transplant (RR 65%, CR 20%) and who progressed after ASCT and who had not received prior BV (RR 70%, CR 20%), were similar. Progression-free survival at 6 months for all patients was 74%. Given the important role of PDL-1 overexpression as part of the underlying pathophysiology of cHL, PD-1 antibodies will play an increasingly important role in treatment and offer important benefit to patients whose cHL has recurred after transplant and for those for whom transplant is not indicated.

Patients with relapsed or refractory Hodgkin lymphoma		
Line of Therapy	ASCT eligible	Not eligible for transplant (age >70)
1st-Line	Salvage therapy + ASCT (responding patients)	Salvage, non-cross-resistant chemotherapy or radiation (note brentuximab vedotin not funded for this population)

Patients with relapsed or refractory Hodgkin lymphoma		
Line of Therapy	ASCT eligible	Not eligible for transplant (age >70)
Maintenance	Brentuximab vedotin currently not funded in most provinces	Not applicable
2nd-Line	Brentuximab vedotin	No funded or effective alternative

2.4 Other Patient Populations in Whom the Drug May Be Used

Current trials are evaluating the impact of the addition of brentuximab vedotin to primary therapy in patients with advanced stage HL, and as a component of induction therapy prior to transplant, either in combination or in the setting of poor response to standard platinum-based salvage treatment. These patients would be appropriate candidates for a PD1 antibody at the time of progression after transplant. Similarly, a funding and therapy gap exists for patients who are not eligible for ASCT because of age or comorbidities, or because salvage therapy has not produced sufficient response; these patients are not currently eligible in many provinces for BV treatment. Given the excellent toxicity profile reported in phase II trials of PD1 antibodies, and the similarity in response rate and time to progression across subgroups reported for nivolumab and pembrolizumab, treatment with a PD1 antibody would be of benefit in this population which has an unmet medical need for additional, more effective and less toxic treatment alternatives.

3 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

One patient advocacy group, Lymphoma Canada provided input on nivolumab for the treatment of patients with classical Hodgkin lymphoma (cHL).

Lymphoma Canada (LC) conducted two anonymous online surveys for patients and caregivers and collected responses from June 5th to 30th, 2017. Responses from an additional survey of patients who have direct experience with nivolumab were collected from September 19th – October 10th, 2017. The links to the surveys were sent via e-mail to patients and caregivers registered on the LC database. The links were also made available via LC Twitter and Facebook accounts, as well as through HL patient forums, other HL-dedicated social media pages and groups, and international lymphoma organizations own contacts.

A total of 101 patient and 15 caregiver respondents provided input to LC. Of those who responded, there were 15 patient respondents who had experience with nivolumab. Please see the Table 1 below listing participants by country and those with/without nivolumab experience who participated in the surveys.

Table 1: Respondents by Country

Respondents	Canada	USA	UK	EU	Other	Skipped	Total
Patients WITH nivolumab experience	7	3	-	2	**3**	**-**	**15**
Patients WITHOUT nivolumab experience	36	4	12	6	8	20	**86**
Caregivers	5	2	4	1	-	3	**15**

For patient respondents who provided information about their demographic information (81/101), 53% live in Canada. Of the 80 respondents who provided information about their gender and age, 70% are female, and 88% are between 20-59 years-old, see Table 2.

Table 2: Gender and age of survey and interview respondents

Respondents	Age Range					Gender		
	< 20	20-39	40-59	≥ 60	Did not answer	Female	Male	Did not answer
Patients WITH nivolumab experience	0	10	4	1	0	9	6	0
Patients WITHOUT nivolumab experience	2	32	22	9	21	47	18	21
Caregivers	0	2	7	3	3	9	3	3
Total	**2**	**44**	**33**	**13**	**24**	**65**	**27**	**24**

The surveys designed by LC had a combination of multiple choice, rating and open-ended questions. There was also skipping logic was built into surveys allowing respondents to be asked questions that were only relevant to them. The open-ended responses to surveys that reflected the sentiment of a majority were included verbatim to provide a deeper understanding of patient and caregiver perspectives.

From a patient's perspective, there are a number of symptoms associated with HL that impact quality of life, which include fatigue or lack of energy, enlarged lymph nodes, drenching night sweats, itching, persistent cough and mental and emotional problems such as anxiety and difficulties with concentrating. Respondents also reported on aspects of their life negatively impacted by HL, including ability to work, personal image, family obligations, intimate relations, friendships and ability to attend school. Most respondents indicated that current treatment options (e.g. ABVD, GDP, BEACOPP and MOPP/COPP, radiation, stem cell transplant, BV and surgery) work well in managing their HL symptoms. LC noted that toxicity associated with their previous treatments were of great concern to many respondents; specifically, fatigue, "chemo-brain", peripheral neuropathy, loss of menstrual periods, thyroid dysfunction, sterility and lung damage were the most commonly reported. LC also indicated that respondents also experienced one or more late or long-term treatment-related side effect (lasting longer than 2 years or appearing later than 2 years after the end of treatment). In the current sample LC noted that 93% of respondents had been treated with at least one line of conventional and 16% of respondents had received ≥ 3 lines of therapy. Respondents who have not experienced nivolumab expect that it demonstrates "effectiveness" (i.e., offer disease control and remission) followed by "minimal side effects" or "less side effects than current treatments". Respondents who have experience with nivolumab reported few side effects, and that they were tolerable. Some of the side effects reported with nivolumab included fatigue, muscle or joint pain, diarrhea, constipation, headache, shortness of breath, rash and back pain. The most common reason for choosing treatment with nivolumab was that there were no other treatment options available. At the time of the survey, LC reported that four respondents were no longer being treated with nivolumab (two had completed their full course of treatment; one respondent did not respond to the drug; and one respondent proceeded to allogeneic transplant after achieving a complete response with

nivolumab). The majority responded that nivolumab had positively impacted their health and well-being, notably no negative impacts on school and family obligation had been experienced. Respondents also reported that nivolumab had positive impacts on their ability to work, attend school, travel, participate in activities, and on their personal relationships.

Please see below for a summary of specific input received from LC. Quotes are reproduced as they appeared in the survey, with no modifications made for spelling, punctuation or grammar. The statistical data that was reported have also been reproduced as is according to the submission, without modification.

3.1 Condition and Current Therapy Information

3.1.1 Experiences Patients have with classical Hodgkin Lymphoma

According to LC, 70% (n = 71/101) of patient respondents who completed the survey or participated in an interview were a teenager or young adult (13-39 years-old) when they were diagnosed with HL.

LC indicated that respondents with HL reported that the symptoms associated with their disease could significantly impact their quality of life. Of particular note, the most commonly reported symptoms include: fatigue or lack of energy (72%), enlarged lymph nodes (68%), drenching night sweats (44%), itching (43%), and persistent cough (38%). Other symptoms affecting quality of life for > 10% of respondents included unexplained weight loss, loss of appetite, trouble breathing, fever and chills and chest pain. Ongoing fatigue (constant, lasting fatigue or waves of fatigue) was also reported by 63% of respondents who were surveyed.

LC also examined which aspects of patients' lives had been negatively impacted by HL. Notably, the majority of patient respondents (61%) indicated that HL had a negative impact on their ability to work. Additional responses are summarized in Table 3.

Table 3: Effect of HL on day-to-day life of patients

Aspect of life NEGATIVELY impacted by HL	# of respondents (total = 83)	% of respondents
Ability to work	51	61%
Personal Image	39	47%
Family obligations	38	46%
Intimate relations	31	37%
Friendships	30	36%
Ability to attend school	13	16%
None of these	11	13%

Many respondents also reported that their quality of life was negatively affected by mental and emotional problems associated with their disease (Table 4).

Table 4: Effect of HL on current quality of life of patients		
Symptom or problem related to HL	**# of respondents (total = 88)**	**% of respondents**
Anxiety/worry	42	48%
Problems concentrating	32	37%
Loss of sexual desire	29	33%
Stress of diagnosis	25	29%
Difficulty sleeping	25	29%
Memory loss	25	29%
Depression	20	23%
None of these	10	11%

Below are some of the key comments gathered from three (3) respondents to help illustrate the impacts in regards to their experience with HL:

- *"I experience more fatigue than I used to and although I'm able to work, I'm exhausted at the end of the day. Exercise is difficult to do on a weekday."* Female, 21-39, USA
- *"I immediately lost my job, as I worked in an environment not safe for someone with a compromised immune system. I had to give up my study at uni, and both devastated me. I was very fit, but now if I try to exercise at the same level I become exhausted very easily. It's very hard."* Female, 21-39, Australia
- *"I almost feel like I suffer from ptsd from this experience. I went into remission for about a year and then had a recurrence. I'm always worried it might come back. If I smell alcohol swabs - like they use before taking blood or administering chemo - my mind goes right back to treatment days - and that's more than 25 years ago."* Female, 50-59, Canada

3.1.2 Patients' Experiences with Current Therapy for classical Hodgkin Lymphoma

LC reported that all patient respondents had previously received treatment or were currently undergoing treatment. Of the patient respondents who did not have experience with nivolumab, 73 patient respondents provided responses regarding their treatments as follows: 93% of respondents had been treated with at least one line of conventional chemotherapy and 16% of respondents had received ≥3 lines of therapy. The most common conventional chemotherapy regimen received was ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) (81%), followed by GDP (gemcitabine, dexamethasone, cisplatin) (10%), BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone) (8%), and MOPP/COPP (mechlorethamine/cyclophosphamide, vincristine, procarbazine, prednisone) (5%). Other types of treatment that respondents had received included radiation therapy (50%), autologous stem cell transplant (26%), brentuximab-vedotin (14%), surgery (10%), allogeneic stem cell transplant (4%), and CAR-T therapy (1%).

In terms of treatment phases, LC indicated that of 85 respondents without nivolumab experience who reported on their treatment phase, 60% of respondents are in remission following their most recent line of therapy, 27% of respondents have been in remission for longer than 5 years and 15% of respondents had previously relapsed after one or more lines of therapy. When LC asked respondents to rate their level of agreement with the statement "*My most recent therapy could manage my Hodgkin lymphoma symptoms*", on a 10-point scale; 10 = strongly agree, 72% of respondents gave a rating of ≥7, indicating that their most recent treatment was able to manage most or all of their HL symptoms.

Regarding side effects of current treatments, LC noted that the toxicity associated with their previous treatments was of great concern to many respondents. The most common side effects respondents experienced during their HL treatments are listed in Table 5. In particular, respondents noted that nausea/vomiting (25/50; 50%), fatigue (23/50; 46%), and hair loss (11/50; 22%) were the most difficult side effects to tolerate. Many respondents (66) also experienced one or more late or long-term treatment-related side effect (lasting longer than 2 years or appearing later than 2 years after the end of treatment). Fatigue (65%), "chemo-brain" (59%), peripheral neuropathy (32%), loss of menstrual periods (23%), thyroid dysfunction (18%), sterility (15%) and lung damage (14%) were the most commonly reported.

Table 5: Side effects of current HL therapies

Side effect	# of respondents (total = 74)	% of respondents
Fatigue	70	95%
Hair loss	67	91%
Nausea/vomiting	65	88%
Mouth sores	51	69%
Peripheral neuropathy	39	53%
Low platelets	36	48%
Anemia and/or	34	46%
Diarrhea	33	45%
Skin rashes/severe itching	29	39%
Loss of menstrual periods	26	35%
Breathing difficulties	23	31%
Infections	23	31%
Back pain	22	30%
Cough	20	27%
Irregular heartbeat	15	20%
Bowel obstruction	12	16%
Viral reactivation (e.g.	9	12%

LC asked respondents to rate how specific aspects of their treatment impacted their quality of life (Table 6). Respondents reported that fatigue had the greatest impact on their quality of life.

Table 6: Negative impact of specific aspects of treatment				
Aspect of treatment	**Weighted average**	**% who rated 7-10 (significant impact)**	**% who rated Not applicable**	**Total number of responses**
Treatment-related fatigue	7.5	80%	0%	74
Ability to tolerate treatment	6.6	59%	0%	74
Infusion reaction	6.3	55%	8.5%	71
Infusion time	6.3	54%	6.8%	74
Number of clinic visits	6.2	59%	0%	73
Number of infections	4.3	22%	10%	73
Frequency of infections	4.0	15%	11%	74

LC also asked respondents to rate the negative impact of previous treatments on specific aspects of day-to-day life; respondents reported that their treatments had the greatest impact on their ability to undertake activities and travel (Table 7).

Table 7: Negative impact of previous treatments on quality of life				
Aspect of life	**Weighted average**	**% who rated 7-10 (significant impact)**	**% who rated Not applicable**	**Total number of responses**
Ability to attend school	8.86	24%	66%	74
Ability to work	7.89	69%	14%	74
Travel	7.47	75%	7%	73
Activities	7.35	76%	1%	74
Intimate relations	7.08	68%	5%	71
Family obligations	6.14	55%	3%	74
Friendships	5.76	54%	0	74

Below are some key comments by four (4) respondents regarding their experience with current therapies:

- *"The chemotherapy I received before and with my bone marrow transplant put me into premature menopause (i'm in my 20s) and that has negatively affected my intimate relations."* Female, 21-39, USA
- *"My short term memory from chemo is very bad on some days, which effects me at work and home. I'm constantly tired, I work full time and have 4 children. One of whom I was pregnant with when diagnosed."* Female, 21-39, UK
- *"I was unable to finish the first semester of nursing school at the time. I was unable to help coach basketball because of low self-esteem from hair loss and fatigue. Did not really want to go places and visit friends because of hair loss."* Female, under 20, USA

- *"Unable to work due to long-term side effects of chemotherapy. Pain and muscle weakness. I'm constantly exhausted, dialed from my stem cell transplant, have issue taking care of my toddler without help."* Female, 21-39, USA

LC also examined how difficult it was for patients to access treatment in their own community: The majority, 59/74 (79%) of respondents, were able to access treatment in their own community. For those who could not access treatment in their own community (n=15), 73% of respondents lived in a community without a cancer centre, or the treatment was not available in their province (20%) or country (7%). The most commonly reported financial impact of treatment was absence from work or school (48/70; 69%). Other financial burdens included parking (40%), cost of medications (30%), and travel to and from appointments (29%).

Below are some key comments by two (2) respondents regarding treatment access:

- *"Medications cost me over $80,000 over the last 7 years to help deal with side-effects of chemo. I am now on long-term disability, because I cannot work."* Female, 20-39, Canada

- *"Absence from work caused me to get into debt, first and second time."* Female, 50-59, UK

Furthermore, LC enquired about patients' choice of treatment. Respondents were asked how important it is for them and their physician to have a choice in deciding which drug to take based on known side effects and expected outcomes with a rating scale of 1 signifying not important as long as there is at least one treatment choice, to 10 signifying as extremely important to have a choice of treatment. LC reported that 70/85 (82%) of respondents rated the importance as 7, 8, 9 or 10, with a weighted average of 8.5. Of 85 respondents without nivolumab experience, 54% reported that they would take a drug with known side effects, potentially serious, if their doctor recommended it was the best choice for them (No = 2%; I don't know = 44%), indicating that many would be willing to tolerate significant side effects if the treatment is effective.

3.1.3 Impact of classical Hodgkin Lymphoma and Current Therapy on Caregivers

There were fifteen (15) caregiver respondents who completed the survey to address the impact on day-to-day life and challenges caregivers face with this type of cancer. Respondents were asked to rate on a scale of 1 (no impact) to 10 (very significant impact) how caring for a person with HL has impacted their day-to-day life. Please see Table 8 below on the impacts on caregivers' daily activities; caregiver respondents reported that a significant impact on their quality of life was their ability to concentrate.

Table 8: Effects of caregiving on quality of life

Daily activity (Total responses = 15)	7-10 (significant
Ability to concentrate	10 (67%)
Contribute financially to household	9 (60%)
Travel	9 (60%)
Attend to household chores	8 (53%)
Volunteer	8 (53%)
Spend time with family and friends	7 (47%)
Exercise	5 (33%)

Table 8: Effects of caregiving on quality of life	
Daily activity (Total responses = 15)	**7-10 (significant**
Fulfill family obligations	4 (27%)

Below are some key comments as described by three (3) caregiver respondents:

- *"My 20 year old son was diagnosed with hl. This last year has been a nightmare. Family, friends don't call or even know what to say. We are left alone, while everyone's life continues."* Female, 40-59, USA
- *"I was pregnant with twins while caring for my man and we did what we had to do and we stuck together. It was hard to be away from our older kids when he was receiving treatments but nurses in oncology dept. are angels."* Female, 20-39
- *"I've become a caregiver. Scheduling my daughter's appointments, managing her medicine. Taken over her care. She was in between jobs at diagnosis and her prospects for a new job has significantly decreased. We support her financially now."* Female, over 60, Canada

3.2 Information about the Drug Being Reviewed

3.2.1 Patient Expectations for and Experiences To Date with nivolumab

Based on no experience using the drug:

Regarding respondents' expectations about the new drug under review: "effectiveness" was most important to 31/44 (70%) patient respondents. A large number of patient respondents (57%) also reported that "minimal side effects" or "less side effects than current treatments" was very important to them.

3.2.2 What Experiences Have Patients Had To Date with nivolumab?

Based on experience using the drug:

LC reported that fifteen (15) HL patient respondents had experience with nivolumab completed the surveys. Seven respondents (47%) live in Canada, 60% are female, and 67% are young adults (ages 20-39). Fifty-three percent (53%) are working full- or part-time, 20% are on long-term disability or are unemployed and 13% are homemakers.

Table 9: HL Patients with nivolumab experience						
Patient	**Gender**	**Age**	**Location**	**Date of dx**	**Access to drug**	**Date started nivolumab**
1	Male	20-39	Russia	2003	2017/07	Paid out-of-pocket
2	Male	20-39	Canada	2009	2017/04	Private insurance
3	Female	40-49	Canada	2012	2015/03	Clinical trial
4	Male	20-39	Australia	2014	2015/08	Drug manufacturer
5	Female	20-39	Canada	2013	2016/10	Drug manufacturer
6	Male	20-39	Belgium	2014	2017/06	Clinical trial
7	Female	20-39	USA	2013	2015/02	Private insurance
8	Female	40-49	Australia	2013	2017/07	Hospital
9	Female	50-59	Canada	2010	2015/07	Clinical trial

Table 9: HL Patients with nivolumab experience						
Patient	**Gender**	**Age**	**Location**	**Date of dx**	**Access to drug**	**Date started nivolumab**
10	Female	20-39	USA	2014	2015/06	Clinical trial
11	Male	40-49	USA	2015	2017/01	Private insurance
12	Female	40-49	Canada	2005	2016/01	Drug manufacturer
13	Female	20-39	Hungary	2009	2014/12	Clinical trial
14	Male	20-39	Canada	----	2015/02	Clinical trial
15	Female	20-39	Canada	2010	2016/01	Clinical trial

In terms of previous therapies, all fifteen (n=15) respondents had received at least 3 lines of therapy and 40% had received 5 or more lines of therapy prior to receiving nivolumab. Previous chemotherapy regimens included ABVD (n=14), ICE (n=6), DHAP (n=5), GDP (n=4), Mini-BEAM (n=3), GEV (n=2), COPP (n=2), bendamustine (n=2), pembrolizumab (n=1), and brentuximab-vedotin (n=11). Fourteen of fifteen patients (93%) had undergone an autologous stem cell transplant, 2 (13%) had undergone an allogeneic stem cell transplant and 10 (71%) had received radiation therapy.

LC asked respondents about their reasons for beginning treatment with nivolumab. The most common reason given for choosing nivolumab treatment was that there were no other treatment options available (11/15; 73%). Eleven of Fifteen respondents (11/15; 73%) were still receiving treatment with nivolumab. Of the 4 respondents who were no longer being treated with nivolumab, 2 had completed their full course of treatment, 1 patient's HL did not respond to the drug and 1 patient proceeded to allogeneic transplant after achieving a complete response with nivolumab.

LC also enquired about which HL symptoms were managed by nivolumab. Of the 12 respondents who were experiencing symptoms before treatment with nivolumab, 6 (50%) reported that nivolumab was able to manage all their disease symptoms. Respondents who were experiencing symptoms of HL when they began treatment with nivolumab reported the following:

Table 10: Effect of nivolumab on HL symptoms (n=12)	
Disease symptom	**Managed by nivolumab**
Fatigue/lack of energy	6/9 (67%)
Enlarged lymph nodes	5/6 (83%)
Enlarged spleen	3/3 (100%)
Frequent infections	2/2 (100%)
Weight loss	4/5 (80%)
Night sweats	5/5 (100%)
Increasing lymphocyte count	5/5 (100%)
Shortness of breath	2/3 (67%)
Fever	3/3 (100%)
Pain	3/3 (75%)

When LC asked about side effects experienced with nivolumab and 5/15 (33%) of respondents reported they did not experience any side effects due to nivolumab treatment, see Table 11.

Table 11: Side effects experienced with nivolumab	
Side effect	**# of responses**
Fatigue	6 (40%)

Table 11: Side effects experienced with nivolumab	
Side effect	**# of responses**
I did not experience any side effects	5 (33%)
Muscle or joint pain	3 (20%)
Diarrhea	3 (13%)
Constipation	(13%)
Headache	(13%)
Shortness of breath	(13%)
Back pain	(13%)
Rash	(7%)
Upper respiratory infection	(7%)
Lung problems	(7%)
Itching	(7%)
Cough	(7%)
Stomach pain	(7%)
Other (hypothyroidism)	(7%)
Low blood counts	0
Nausea/vomiting	0
Fever	0
Infusion reactions	0
Peripheral neuropathy	0

When prompted to compare how nivolumab with previous therapies, with respect to side effects, 3 individuals provided the following comments:

- *"It's an amazing drug. Short infusion time, low side effects, no pre-meds needed to control nausea, no hair loss. Has made active treatment way more tolerable than any previous regime." Female, 20-39, Canada*

- *"Outstanding. The best I have felt in 7 years. Start my 11th infusion next week." Male, 20-39, Canada*

- *"Easy low maintenance treatment that ultimately stopped working for my lymphoma but was super easy to tolerate." Female, 20-39, USA*

LC asked respondents about patients' day-to-day life and quality of life with nivolumab. Respondents were asked to rate, on a scale of 1-10 (1=significant negative impact; 10=significant positive impact), how nivolumab has affected different aspects of their life. Based on the ratings (Table 12), LC reported that nivolumab had a positive impact on respondents' ability to work, attend school, participate in activities, travel and their personal relationships.

Table 12: Side effects experienced with nivolumab					
Aspect of life	**Weighted average**	**Positive Impact (rating = 7-10)**	**Rating = 10**	**Negative impact (rating = 1-4)**	**Not applicable**
School	9	3 (20%)	3 (20%)	0	12 (80%)
Family	8.3	13 (87%)	9 (60%)	0	1 (7%)
Activities	7.9	14 (93%)	9 (60%)	2 (13%)	0
Travel	7.8	10 (67%)	7 (47%)	1 (7%)	3 (20%)
Friendships	7.8	10 (67%)	8 (53%)	1 (7%)	3 (20%)

Table 12: Side effects experienced with nivolumab					
Aspect of life	**Weighted average**	**Positive Impact (rating = 7-10)**	**Rating = 10**	**Negative impact (rating = 1-4)**	**Not applicable**
Intimate relations	7.7	10 (67%)	7 (47%)	1 (7%)	2 (13%)
Work	7.5	8 (53%)	7 (47%)	1 (7%)	4 (27%)

LC also asked respondents based on their experience with nivolumab, if they would recommend this treatment to other HL patients. All 15 respondents (100%) stated "yes".

Below are some key comments described by four (4) respondents when asked how nivolumab has changed their health and well-being:

- *"For almost two years now Opdivo has allowed me to live a full and active life with my family and friends with very little down time after each treatment." Female, 40-49, Canada*

- *"I can not fully describe to you the positive effects of being able to receive this treatment. It… is the reason I am here today and able to complete this survey. I am alive today due to this treatment. I am alive today with the quality of life that is not seen with people getting treatment for CA. This opportunity for others should not be out of reach due to cost of medication. That would be inhumane." Male, 20-39, Canada*

- *"I am grateful for the opportunity… to be part of the trial. I was stage 4 with a 20cm tumor wrapped around my heart. A year on the drug, I hit CR. I stayed on treatment for another year and remained in CR. I have been almost 3 months off and I feel no symptoms… This drug needs to be approved and funded and available to every cancer center in Canada. I truly believe that I would not be alive and well today—now back to work and trying to rebuild a financial future—if it were not for Nivolumab." Female, 50-59, Canada*

- *"Opdivo let me live!! I believe that everyone should have affordable access to this amazing drug! I felt wonderful for two years! I was able to be a wife, a mom, a volunteer, friend, daughter, sister, and return to work." Female, 20-39, USA*

3.3 Additional Information

None provided.

4 SUMMARY OF PROVINCIAL ADVISORY GROUP (PAG) INPUT

The Provincial Advisory Group includes representatives from provincial cancer agencies and provincial and territorial Ministries of Health participating in pCODR. The complete list of PAG members is available on the pCODR website. PAG identifies factors that could affect the feasibility of implementing a funding recommendation.

Overall Summary

Input was obtained from all of the provinces participating in pCODR. The following were identified

as factors that could impact the implementation:

Clinical factors:

- New treatment option for relapsed or refractory classical Hodgkin Lymphoma (HL)
- Clarity on eligible patients

Economic factors:

- New treatment option
- Chair time

Please see below for more details.

4.2 Factors Related to Comparators

PAG noted that there is no standard of care for patients with HL who have failed autologous stem cell transplant, except brentuximab vedotin where funding is available. After failure of brentuximab vedotin, chemotherapy with palliative intent, best supportive care and clinical trials are options.

4.3 Factors Related to Patient Population

There is an unmet need for relapsed or refractory classical HL. PAG is seeking clarity on the eligible patients. PAG noted that the trial is for patients with classical HL who have failed autologous stem cell transplant and there were three cohorts in the trial.

PAG noted there may be requests for nivolumab in patients with other subtypes of HL and in patients who have not had or were ineligible for an autologous stem cell transplant. PAG is seeking guidance on whether the data could be generalized to these groups of patients.

PAG is seeking guidance on the use of nivolumab in patients who have failed brentuximab vedotin or other treatments post-transplant. PAG is also seeking clarity on the place of therapy of nivolumab, specifically guidance on sequencing with brentuximab vedotin if nivolumab is an additional line of therapy (i.e. the sequencing order of brentuximab vedotin and nivolumab if both are options) or whether nivolumab would be considered in place of brentuximab vedotin (i.e. a choice of one or the other).

Pembrolizumab for classical HL is under review at pCODR at the time of this PAG input. PAG noted that the patient population for pembrolizumab is different than nivolumab and is seeking information on comparison of nivolumab and pembrolizumab.

4.4 Factors Related to Dosing

The dose for HL is 3 mg/kg administered IV over 60 minutes (new information may reduce this to 30 minutes) every 2 weeks until progression or unacceptable toxicity. PAG is seeking information on the appropriateness of using cost saving dosing strategies of 3mg/kg up to a dose cap of 240mg every two weeks and 6mg/kg up to a dose cap of 480mg every four weeks.

4.5 Factors Related to Implementation Costs

As nivolumab is an intravenous therapy, additional resources would be required to prepare and administer nivolumab. PAG noted that nivolumab is administered every two weeks whereas both pembrolizumab and brentuximab vedotin are administered every three weeks.

PAG noted that there would be drug wastage with the weight based dose but identified this would

be minimized with the two different vial sizes and with vial sharing, given that nivolumab is currently used for many other indications. A dose cap of 240 mg would avoids drug waste for all patients 80 kg and over.

The treatment duration is until disease progression. PAG is seeking information on the mean and the range of treatment duration.

4.6 Factors Related to Health System

Nivolumab would be administered in an outpatient chemotherapy center for appropriate administration and monitoring of toxicities. As nivolumab is a high cost drug and requires monitoring of immune-mediated reactions post-infusion, PAG noted that smaller outpatient cancer centres may not have the expertise and resources to administer nivolumab. This is a barrier for those patients who will need to travel to larger cancer centres that have the resources and expertise to administer nivolumab.

4.7 Factors Related to Manufacturer

None identified.

5 SUMMARY OF REGISTERED CLINICIAN INPUT

Two group clinician inputs were provided.

The clinicians providing input indicated that nivolumab would be an additional line of therapy for patients who have relapsed disease following stem cell transplant and Brentuximab vedotin (BV) and who have no other effective options. They noted that nivolumab offers patients hope of long term cure, given the high response rates and remissions. The magnitude of benefits allows patients, who are typically 20 to 30 years old, to return to work and enjoy an excellent quality of life. The side effects are as expected for immunotherapies and are manageable by clinicians who are used to dealing with immune-related adverse events

Please see below for details from the clinician inputs.

5.2 Current Treatment(s) for classical Hodgkin Lymphoma

There is no standard treatment for patients with classical Hodgkin lymphoma that have failed autologous stem cell transplant. BV is approved in this setting and the most common agent used, although it is not standard of care as Health Canada approval was granted as NOC with conditions (NOC/c). If the patient had received prior BV, subsequent treatments include chemotherapy, radiation therapy, supportive care and some centres may offer allogeneic stem cell transplant to suitable patients.

One clinician providing input noted that BV is also under review as consolidative treatment post-ASCT based on superior PFS and data is emerging of efficacy in primary therapy setting. Thus, patients that have been previously exposed to BV represent an unmet medical need in this young, at risk population. Of note, allogeneic transplant can be considered following ASCT failure, however, it typically is only effective in late relapses with chemosensitive disease and, the treatment related mortality approaches 30%.

5.3 Eligible Patient Population

One clinician providing input indicated that there would be a small number of patients who would be eligible for nivolumab. Approximately 90% and 80% of patients with limited stage and advanced stage HL, respectively, are cured with the current standard of care. While HL is the most common lymphoma in adolescents and young adults, it remains a relatively uncommon lymphoma overall.

The group of clinicians providing input estimated that approximately 20 patients per year may qualify fornivolumab in Ontario, based on ASCT numbers for cHL at a large academic cancer centre with extrapolation to the province of Ontario and assuming 50% relapsed rate.

5.4 Identify Key Benefits and Harms with Nivolumab

The clinicians providing input noted that nivolumab is a PD1 inhibitor which is effective across a range of malignancies. However, given the underlying biology of cHL with frequent PD-L1 expression, the efficacy of nivolumab in this disease has generated the highest overall response rate of any tumour. The objective overall response rate is approximately 60-70% and more than 90% of patients have some degree of tumour regression. It is clear from studies that patients with complete response have the most durable remissions (approximately 2 years), however even partial response and stable disease results in a median PFS of 15 months and 11 months, respectively. It is anticipated that a proportion of patients are cured with PD1 inhibitors, similar to what is seen in solid tumours like melanoma, however longer follow-up will be needed to confirm this. Quality of life also has a significant improvement. The side effects are as expected for a PD1 inhibitors with less than 5%

having grade 3/4 adverse events and is manageable by clinicians who are used to dealing with immune-related adverse events. The clinicians note that it is unusual for patients to discontinue therapy due to toxicity.

5.5 Advantages of Nivolumab Over Current Treatments

The clinicians providing input identified that following BV failure, the only standard option is palliative chemotherapy, which has low response rate and short duration of remissions. They noted that PD1 inhibitors demonstrated clear superiority over standard chemotherapy in this fourth line setting but recognized that there are no comparative data from Phase 2 trial.

They noted that the data in BV naïve patients are also encouraging, with the PFS overall superior (18 months) compared with similar population treated in phase 2 with BV (5.6 months). Ongoing studies right now will determine whether PD1 inhibitors are superior to BV in BV naïve patients. Regardless, in BV treated patients whether it is through recurrence following transplant or consolidative therapy after transplant, PD1 inhibitors like nivolumab are the clear choice to improve long term survival and potentially over cure to patients. There will be some patients with residual side effects from prior chemotherapy such as peripheral neuropathy and neutropenia, where PD1 inhibitors would be a preferred choice over BV. Of note, as BV moves into earlier stages of disease (e.g. Echelon 1), there will be very few 'BV naïve 'patients, thus making access to PD1 inhibitors crucial for this patient population.

5.6 Sequencing and Priority of Treatments with Nivolumab

The clinicians providing input indicated that nivolumab would be an additional line of therapy for patients who have relapsed disease following ASCT and BV and who have no other effective options other than PD1 inhibitors. They noted that this patient population is typically 20 -30 years old and the magnitude of benefit afforded by treatment with PD1 inhibitors allows them to return to work and enjoy an excellent quality of life. In very select patients, it has been shown that nivolumab can be used to bridge to allogeneic HSCT.

5.7 Companion Diagnostic Testing

The clinicians providing input noted that PD-L1 testing is not required as cHL is typified by abundant expression of PD-L1 in almost 100% of patients.

5.8 Additional Information

None.

6 SYSTEMATIC REVIEW

6.1 Objectives

The primary objective of this review is to evaluate the efficacy and safety of nivolumab for treatment of adult patients with Classical Hodgkin Lymphoma (cHL) who have relapsed or progressed after:

- autologous stem cell transplantation (ASCT) and brentuximab vedotin (BV); or
- three or more lines of systemic therapy including ASCT.

Supplemental Questions most relevant to the pCODR review and to the Provincial Advisory Group were identified while developing the review protocol and are outlined in section 7: Summary and critical appraisal of the Manufacturer-submitted indirect treatment comparison of nivolumab to BV and best supportive care (BSC) in relapsed or refractory classical Hodgkin lymphoma after failure of ASCT.

6.2 Methods

6.2.1 Review Protocol and Study Selection Criteria

The systematic review protocol was developed jointly by the CGP and the pCODR Methods Team. Studies were chosen for inclusion in the review based on the criteria in Table 6.1. Outcomes considered most relevant to patients, based on input from patient advocacy groups are those in bold. The literature search strategy and detailed methodology used by the pCODR Methods Team are provided in Appendix A.

Table 6.1: Selection Criteria

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
Published or unpublished RCTs In the absence of RCT data non-randomized or single arm clinical trials investigating the safety and efficacy of nivolumab were included.**	1) patients who failed on ASCT and are BV-naïve (Cohort 1) 2) patients who failed on ASCT and subsequent BV treatment (Cohort 2) 3) patients after failure of ASCT who received BV in any treatment order (Cohort 3) Subgroups: • Sex (male vs. female) • Age • ECOG performance status • Disease stage at baseline	Nivolumab monotherapy	**Cohort 1** - BV - Chemotherapy • Gemcitabine • Vinblastine • Vinorelbine • COPP (cyclophosphamide, vincristine, procarbazine, prednisone) - Best supportive care **Cohort 2 and Cohort 3** - Chemotherapy • Gemcitabine • Vinblastine • Vinorelbine • COPP (cyclophosphamide, vincristine,	Primary • OS • PFS • HRQoL Secondary • ORR • Complete remission • Partial remissions • Stable disease • Progressive disease • DOR • DCR Safety • AEs • SAEs • WDAEs

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
	• Prior lines of BV therapy • Prior BV failure • Prior systemic therapies (yes vs. no) • Extra-nodal involvement • B-symptoms at baseline • Number of prior therapies • Time from the completion of the most recent therapy		procarbazine, prednisone) - Best supportive care	
Abbreviations: AE=adverse events; **ACST** = autologous stem cell transplant; **BV=** brentuximab vedotin **cHL** = classical Hodgkin lymphoma; **CR** = complete response; **DCR**=disease control rate; **DOR=**duration of response; **ECOG**=Eastern Cooperative Oncology Group Performance Status; **HRQoL**=Health related quality of life; **ORR** = overall response rate; **RCT=**randomized controlled trial; **SAE**=serious adverse events; **WDAE**=withdrawals due to adverse events				
Notes: * Standard and/or relevant therapies available in Canada (may include drug and non-drug interventions). **Dose escalation trials were excluded but mixed design clinical trials (i.e. trials with a dose escalation phase followed by an efficacy-determining phase in which the intervention is administered at the same dose and schedule to all patients) were included if data were reported separately for the two phases of the trial.				

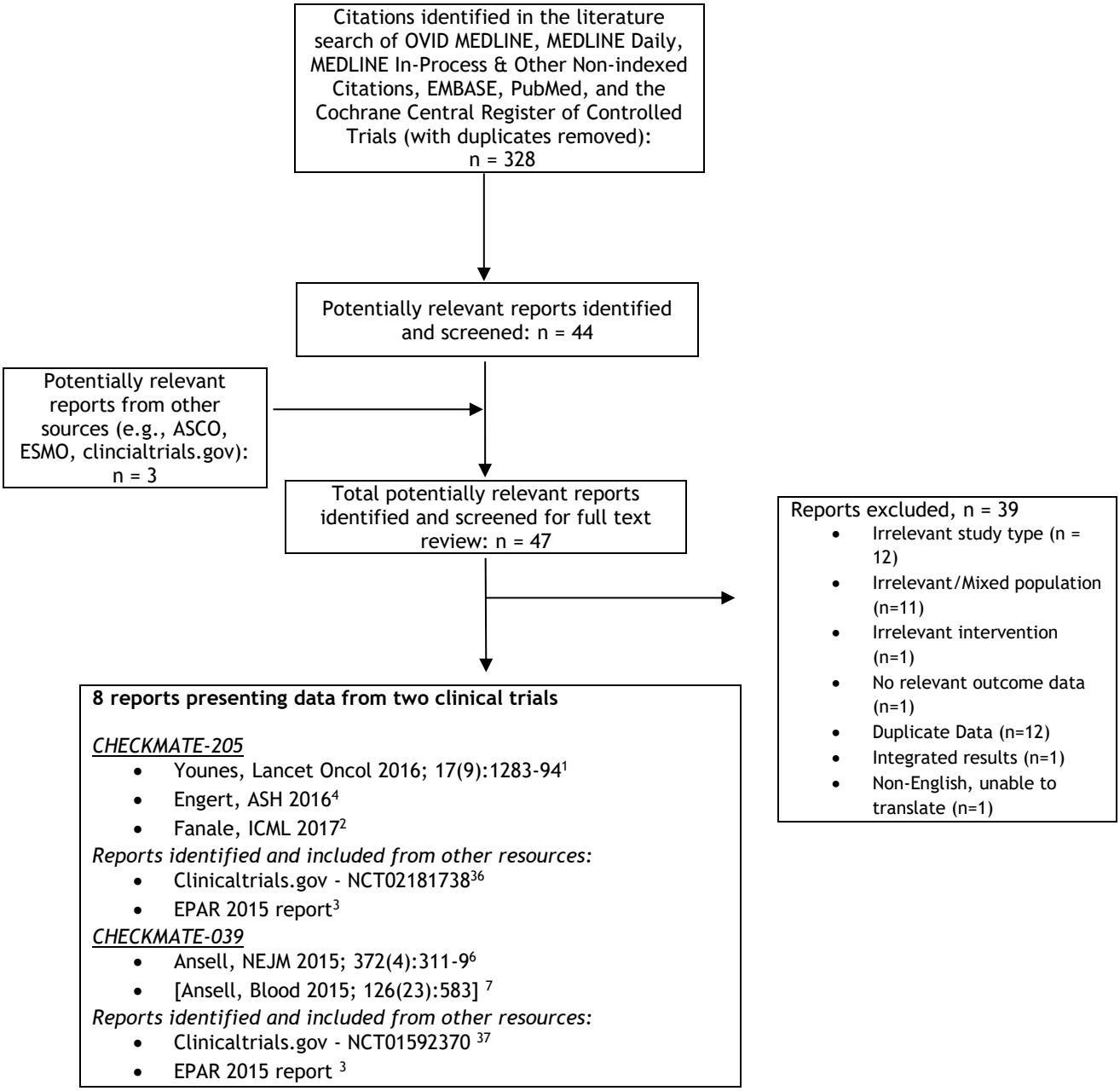
** Standard and/or relevant therapies available in Canada (may include drug and non-drug interventions)*

6.3 Results

6.3.1 Literature Search Results

Of the 47 potentially relevant reports identified, eight reports reporting data from two clinical trials were included in the pCODR systematic review,[1,6] and 39 studies were excluded. Studies were excluded because they did not report the results of a clinical trial design, included irrelevant or mixed study populations, used an irrelevant intervention, or did not report the outcomes of interest. One citation reported integrated safety results from CHAECKMATE-205 and a subgroup of CHECKMATE-039 trials, and one article was published in German. Conference abstracts which reported duplicate data from the included full articles were excluded. If data from the single data-cut-off point was reported in more than one citation, the citation which included more detailed or more recent data was included. Figure 6.1 illustrates the PRISMA flow Diagram for the study selection process.

Figure 6.1: PRISMA Flow Diagram for Inclusion and Exclusion of studies



Note: Additional reports related to CHECKMATE-205 and CHECKMATE-039 trials were obtained from the Submitter : CA209205 CSR,[38] CA209039 interim CSR,[39] CHECKMATE-205 protocol,[40], CONSORT diagrams for CHECKMATE-205 and CHECKMATE-039 trials,[40] Manufacturer's report on the indirect treatment comparisons,[8] Manufacturer's Systematic Review for the efficacy and safety of cHL therapies,[41] BMS Checkpoint Response(20-Nov-2017)[5]

6.3.2 Summary of Included Studies

Two non-randomized trials met the selection criteria of this review. CHECKMATE-205 (n=243) was a non-comparative, multi-cohort, single-arm, open-label, phase 2 study of nivolumab in patients with cHL, that consisted of four cohorts of patients who: had failed on ASCT and were BV-naïve (Cohort A); had relapsed or failed on prior BV treatment as a salvage therapy after failure of ASCT (Cohort B); had prior ASCT and BV in any treatment order (i.e., BV before and/or after ASCT) (Cohort C); or had a newly diagnosed and untreated advanced stage cHL (Cohort D). For the purpose of this pCODR Review, the outcome results of Cohort D will not be presented because it does not align with the funding request. CheckMate039 was a Phase 1, open-label, multicenter, dose-escalation, and multi-dose study to assess the tolerability of nivolumab in patients with relapsed and refractory hematological malignancies, including Hodgkin lymphoma.

Detailed Trial Characteristics

The trials included in this systematic review are compared and contrasted in Table 6.2. Relevant summary information on trial characteristics is also provided in section 2.1.3.

Table 6.2: Summary of Trial Characteristics of the Included Studies

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
Study name CHECKMATE-205 (CA209205)[1,2,4] NCT02181738[36] **Characteristics** Non-Comparative, Multi-Cohort, Single Arm, Open-Label, Phase 2 trial **Sample size** N = 243 (Cohorts A, B, and C) **Locations** 34 sites in 10 countries, including (Austria, Belgium, Canada, Czech Republic, Germany, Italy, the Netherlands, Spain, the United Kingdom, and the United States). **Patient Enrolment Dates** July 2014 – August 2015 (Cohorts A, B, and C) **Estimated Completion date** 01-Oct-2020 **Data cut-off dates** 05-Oct-2015 (Cohort B efficacy) 28-Jun-2016 (Cohort A efficacy) 19-Apr-2016 (Cohort C efficacy) 16-Dec-2016 (Cohorts A, B, and C efficacy and safety)	<u>Key Inclusion Criteria:</u> • Aged ≥ 18 years • ECOG performance status of 0 or 1 Cohorts A, B, C: • History of conditioning chemotherapy followed by ASCT as a part of salvage therapy for cHL • Failed to achieve a response or progressed after ASCT • Failed to achieve a response or progressed after treatment with BV or may be BV naïve Cohort D: • Newly diagnosed (untreated) <u>Key Exclusion Criteria:</u> • Known central nervous system lymphoma • Subjects with nodular lymphocyte-predominant Hodgkin Lymphoma • Prior allogeneic stem cell transplantation (SCT) • Chest radiation within 24 weeks before first study dose • Treatment with carmustine ≥ 600 mg/m²	<u>Intervention:</u> Nivolumab Cohorts A, B, C: Nivolumab 3 mg/kg every 2 weeks Cohort D: Nivolumab: 240 mg every 2 weeks + Doxorubicin: 25 mg/m² + Vinblastine: 6 mg/m² + Dacarbazine 375 mg/m² <u>Comparator:</u> There was no comparator	<u>Primary:</u> ORR by IRRC <u>Secondary:</u> ORR by SI DOR by IRRC and SI CR by IRRC PR by IRRC <u>Exploratory</u> PFS by IRRC and SI OS Safety HRQoL

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
Funding Bristol-Myers Squibb			
Study name CHECKMATE-039)[6,7] NCT01592370[37] **Characteristics** Open-label, multicenter, dose-escalation, and multidose study Phase 1 trial **Sample size** N = 23 **Locations** 7 sites in the United States **Patient Enrolment Dates** December 2012 – November 2013 **Estimated Completion date** December 2018 **Data cut-off dates** 16-Jun-2014 11-Aug-2015 **Funding** Bristol-Myers Squibb	Key Inclusion criteria: • Adult patients (aged ≥18 years) • histologically confirmed evidence of relapsed or refractory Hodgkin's lymphoma with at least one lesion measuring > 1.5 cm • Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1 Key Exclusion Criteria: • history of cancer involving CNS • previous or active autoimmune disease • concomitant second cancer • previous organ allograft or allogeneic bone marrow transplantation.	Intervention: Nivolumab 3 mg/kg at week 1, 4, and every 2 weeks thereafter Comparator: There was no comparator	Primary: Safety • AEs • SAEs • WDAEs • Deaths Secondary: ORR by SI ORR by IRRC Time to response • TTR • Time to CR • Time to PR, DOR PFS Exploratory OS Immunogenicity
Abbreviations: **AEs**= adverse events; **ASCT** = autologous stem cell transplant; **BV** = brentuximab vedotin; **cHL** = classical Hodgkin lymphoma; **CR** = complete remission; **CNS=** central nervous system**; DOR** = duration of response; **ECOG** = Eastern Cooperative Oncology Group; **IRRC**= Independent radiologic review committee; **HRQoL** = health-related quality of life; **SI** = study investigator; **ORR** = objective response rate; **PR**= partial remission; **PFS** = progression-free survival; **OS** = overall survival; **SAE**=serious adverse events; **WDAE**=withdrawals due to adverse events			

Table 5: Select quality characteristics of included studies of nivolumab in patients with cHL

Study	Treatment vs. Comparator	Primary outcome	Required sample size	Sample size	Randomization method	Allocation concealment		Blinding	ITT Analysis	Final analysis	Early termination	Ethics Approval
CHECKMATE-205 [1,2,4]	Nivolumab vs. No comparator	ORR by IRRC	Cohort A (60) Cohort B (60) Cohort C (200)	Cohort A (63) Cohort B (80) Cohort C (100)*	Not randomized	No		No	No	No	No	Yes
CHECKMATE-039 [6,7]	Nivolumab vs. No comparator	Safety	Not calculated	23	Not randomized	No		No	No	No	No	Yes

* The protocol amendment #7 reduced the sample size for cohort C from 200 to 100.

a) Trials

CHECKMATE-205

CHECKMATE-205 was a non-comparative, multi-cohort, single-arm, open-label, phase 2 study of nivolumab in patients with cHL. The primary objective of the trial was to assess the clinical benefit of nivolumab in adult cHL patients who failed to respond to ASCT. The trial was conducted at 34 sites in 10 countries (Austria, Belgium, Canada, Czech Republic, Germany, Italy, the Netherlands, Spain, the United Kingdom, and the United States (US)), and was composed of the following patient cohorts (Figure 6.2). The study cohorts consisted of patients who:

- had failed on ASCT and were BV-naïve (Cohort A);
- had relapsed or failed on prior BV treatment as a salvage therapy after failure of ASCT (Cohort B); or
- had failed ASCT and received BV before ASCT, after ASCT or before and after ASCT (i.e. BV as an initial therapy or salvage therapy before ASCT, and/or BV after ASCT (e.g., salvage and maintenance therapy after ASCT) (Cohort C).

Cohort D was added to the trial (protocol amendment #07, October 21, 2015) to investigate the safety and tolerability of a new nivolumab regimen (i.e., nivolumab monotherapy for four doses, followed by six cycles of nivolumab in combination with chemotherapy) in adult patients with newly diagnosed, previously untreated, advanced stage cHL.[38] For the purpose of this pCODR Review, the outcome results of Cohort D will not be presented because it does not align with the funding request.

To be eligible in this study patient had to be 18 years of age or older, and to have recurrent cHL after failure of ASCT and subsequent BV, previous treatment with BV (not required to be refractory to BV), Eastern Cooperative Oncology Group performance (ECOG) status score of 0 or 1, and either documented failure to achieve at least partial remission after the most recent treatment, or documented relapse (after complete remission) or disease progression (after partial remission or stable disease). Patients also had to have received previous high-dose conditioning chemotherapy followed by ASCT as part of salvage therapy. However, those patients who had

received following treatments were excluded: treatment with BV before the first ASCT (cohorts A and B); ASCT within 90 days of the first dose of nivolumab; previous chemotherapy within 4 weeks, nitrosoureas within 6 weeks, therapeutic anti-cancer antibodies within 4 weeks, radio-immuno-conjugates or toxin immune-conjugates (excluding BV) within 10 weeks, BV within 4 weeks, or major surgery within 2 weeks of the first dose of nivolumab; carmustine at a dose of 600 mg/m^2 or more received as part of the pre-transplantation conditioning regimen; previous radiotherapy within 3 weeks or chest radiation within 24 weeks before the first dose of nivolumab; previous treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody (including ipilimumab or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways); and previous allogeneic stem-cell transplantation.[1] Patients with the following concurrent diseases were also excluded: active interstitial pneumonitis; any serious or uncontrolled medical disorder resulting in an increased risk associated with participation in the study or study drug administration; a prior malignancy active within the previous 3 years (except for locally curable cancers that have been apparently cured); active, known, or suspected autoimmune disease; or conditions requiring systemic treatment with either corticosteroids or other immunosuppressive drugs within 14 days of nivolumab administration.[1]

The study consisted of three phases: screening, treatment, and follow-up. Patients underwent screening evaluations to determine eligibility within 28 days prior to first dose. In the treatment phase, eligible patients received nivolumab 3 mg/kg intravenous (IV) on the first day of each 14-day cycle. Nivolumab was administered until unacceptable toxicity or disease progression (i.e., relapsed disease after CR achieved during the study) or progressive disease (i.e., stable disease attained after PR, during the study) according to the International Working Group criteria for Malignant Lymphoma (2007 IWG) criteria. In the follow-up phase, patients were assessed for response by computerized tomography (CT) or magnetic resonance imaging (MRI) beginning at week 9 (± 7 days) after the drug was initiated and then at weeks 17, 25, 37 and 49 during the first year of treatment. The assessments were then performed every 16 weeks (± 14 days) up to week 97, continuing every 26 weeks (±21 days) beyond week 97, until disease progression is documented. A 18F-fluorodeoxyglucose–positron-emission tomography (FDG-PET) scan was required at screening, weeks 17 and 25 in all enrolled patients, and at week 49 for patients who did not have two consecutive negative FDG-PET scans after week 1 and prior to week 49, and to confirm CR. Patients continued to have tumor assessments in the follow-up period if they discontinued treatment for reasons other than progression, undergoing allogeneic stem cell transplantation, or ASCT. Patients in Cohort C who had persistent CR for one year had a specific follow-up schedule, as they would discontinue the study treatment at the end of first year, with a maximum two years of follow-up, and an opportunity to re-initiate treatment, if they experienced disease relapse.[1,2]

The primary outcome of CHECKMATE-205 trial was objective response rate (ORR), determined by an Independent Radiologic Review Committee (IRRC), and defined as proportion of subjects achieving either a partial remission (PR) or complete remission (CR) according to 2007 IWG criteria.[1,36] Other study outcomes included duration of objective response (DOR), CR rate, duration of CR, PR rate, duration of PR, and progression-free survival (PFS) based on IRRC assessments; ORR, DOR, and PFS based on investigator assessments, overall survival (OS), safety, quality of life with EQ-5D questionnaire and the European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire—Core 30 (EORTC QLQ-C30), 9p24.1 alterations, and PD-1 ligand expression.[1,36]

The trial was planned to include a sample size of 60 patients in Cohort A and Cohort B , which would provide a 93% power to reject the null hypothesis that the true proportion of patients achieving an ORR is ≤20%, assuming an ORR of 40% and given a two-sided type I error (α) of 5%.[1] A sample size of 200 was empirically determined for Cohort C to support expanded assessment of the benefit-risk profile of nivolumab in cHL through observation of less common safety events.[3]

Efficacy and safety analyses were performed in patients who had received at least one dose of nivolumab. The analysis for the primary outcome was performed independently for each cohort after completion of a pre-specified duration of minimum follow-up (i.e., time between the last patient's first treatment and the last patient's last visit or the data cut-off date). The pre-specified minimum follow-up was 9 months for Cohort A, and 6 months for Cohort B and Cohort C.[5]

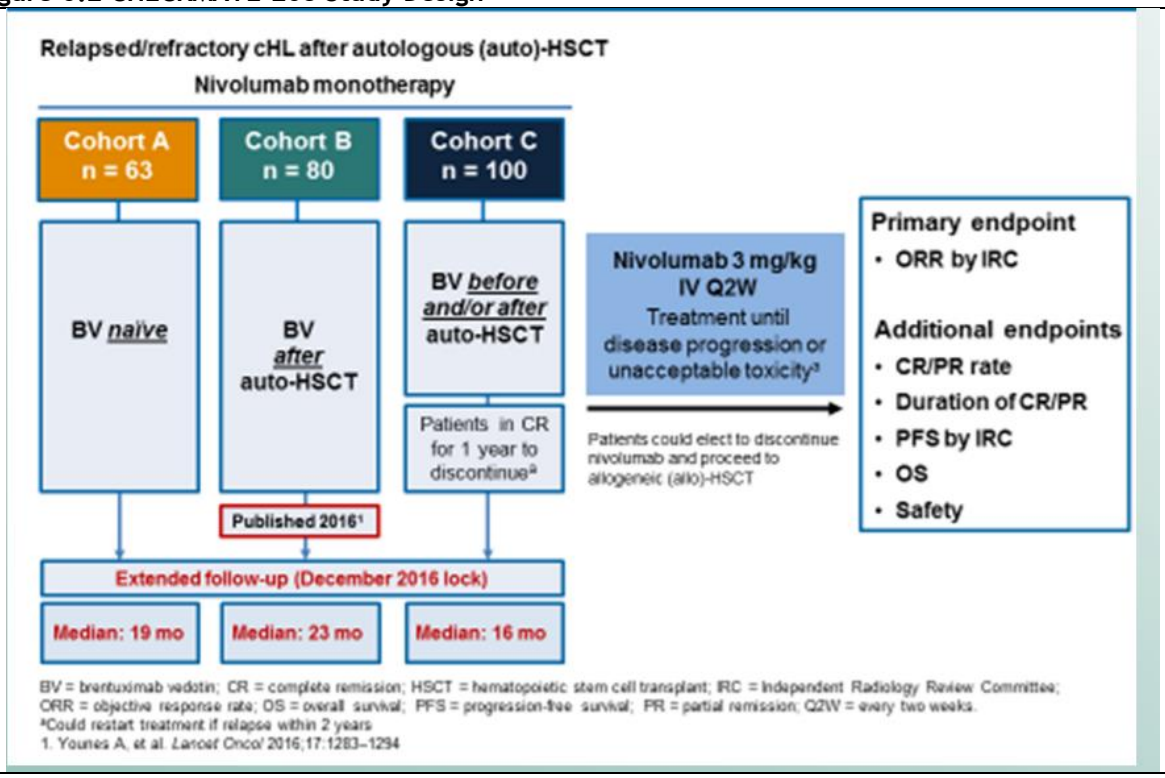
This study is ongoing. Interim analyses of the efficacy and safety outcomes were performed after the minimum follow-up periods (for OS) were reached as follows:[5]

Database lock	Focus	Follow-up	*a priori*	Reason for unplanned database lock
Oct 2015	Cohort B - efficacy	6 months	Yes	
Apr 2016	Cohort C - efficacy	6 months	Yes	
Jun 2016	Cohort A - efficacy	9 months	Yes	
Dec 2016	Updated efficacy and safety	Cohort A (15 months) Cohort B (20.5 months) Cohort C (13.7 months)	No	Commitment to European medical Agency to provide updated efficacy and safety

Source: [Checkpoint document][5]

The original study protocol was published on 25-Apr-2014. The revised protocol (version 04a, dated 08-Sept-2016) incorporated 13 amendments, and 1 administrative letter.[38] The major amendments were related to patient follow-up and the assessment of study outcomes. Based on the first global amendment (amendment #03), the first disease progression assessment would be performed at week 9. In addition, CT or MRI schedules were changed to weeks 9, 17 and 25 during the first 6 months, and the first positron-emission tomography (PET) scan would be performed at week 17 instead of week13. This amendment also permitted patients to continue treatment beyond investigator-assessed disease progression. The administrative letter announced the change of duration of follow-up for the primary endpoint. Amendment #7 added Cohort D to the study and reduced the sample size for Cohort C from 200 to 100. Amendment #10 allowed optional collection of quality of life data (EQ-5D and EORTC QLQ-C30) after discontinuation of study treatment across all study cohorts.

Figure 6.2 CHECKMATE-205 Study Design



Note: Cohort D was added to investigate the overall safety and tolerability of nivolumab monotherapy followed by nivolumab in combination with chemotherapy (doxorubicin, vinblastine, and dacarbazine) in subjects who are newly diagnosed cHL with advanced stage (Stage IIB, III and IV) disease. Results of Cohort D are not included in this CSR. As of December 2016, Cohort D was closed to enrollment (n=51 treated subjects).

Source: [Checkpoint document][5]

CHECKMATE-039

CheckMate039 was a Phase 1, open-label, multicenter, dose-escalation, and multi-dose study to assess the tolerability of nivolumab and the combination of nivolumab and daratumumab, with or without immunomodulatory drugs (pomalidomide and dexamethasone) in patients with relapsed and refractory hematological malignancies, including a cohort of patients with Hodgkin lymphoma. Although this study allowed enrollment for any type of Hodgkin lymphoma including nodular lymphocyte predominant Hodgkin disease, all Hodgkin lymphoma patients who enrolled in the expansion cohort had cHL (n= 23), and all 23 patients received nivolumab monotherapy at 3 mg/kg patient's body weight. The trial was conducted at seven sites in the US.[6]

To be eligible for participation in this study, patients had to be at least 18 years of age, have histologically confirmed evidence of relapsed or refractory Hodgkin lymphoma with at least one lesion measuring more than 1.5 cm, an Eastern Cooperative Oncology Group (ECOG) performance-status score of 0 or 1, previous treatment with at least one chemotherapy regimen, and no

autologous stem-cell transplantation (ASCT) within the previous 100 days. Patients were excluded if they had a history of cancer involving the central nervous system, a history of or active autoimmune disease, a concomitant second cancer, or a previous organ allograft or allogeneic bone marrow transplantation.[6]

The primary objective of CHECKMATE-039 was to evaluate the safety and side-effect profile of nivolumab. Secondary objectives included characterizing the efficacy of nivolumab, based on best overall response (BOR), DOR, ORR, PFS, and OS, and assessing PD-1 ligand loci integrity and expression of the encoded ligands. Adverse events were assessed throughout the study, and for 100 days after administration of the last dose, according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.[6]

CHECKMATE-039 consisted of dose escalation and expansion cohorts. The study design is shown in Figure 6.3. Sample size calculation for the dose escalation phase was not based on statistical considerations, but rather depended on the number of observed toxicities. Between 6 and 9 patients were expected to be treated at each dose (6 + 3 design), starting at 1 mg/kg and escalating to 3mg/kg and 10 mg/kg. The expansion cohort was treated at the maximum tolerated dose (3 mg/kg), determined during the dose escalation phase.[6] Using the Clopper-Pearson method for exact confidence intervals (CI), 16 subjects were planned to be enrolled in each of 5 tumor type groups in the expansion cohort (i.e., Multiple Myeloma, chronic myeloid leukemia, Hodgkin lymphoma, B-cell lymphoma, and T-cell lymphoma). This sample size would ensure 86% chance of observing ≥ 2 responses, and 65% chance of observing ≥3 responses, if the true ORR was 20%.[6]

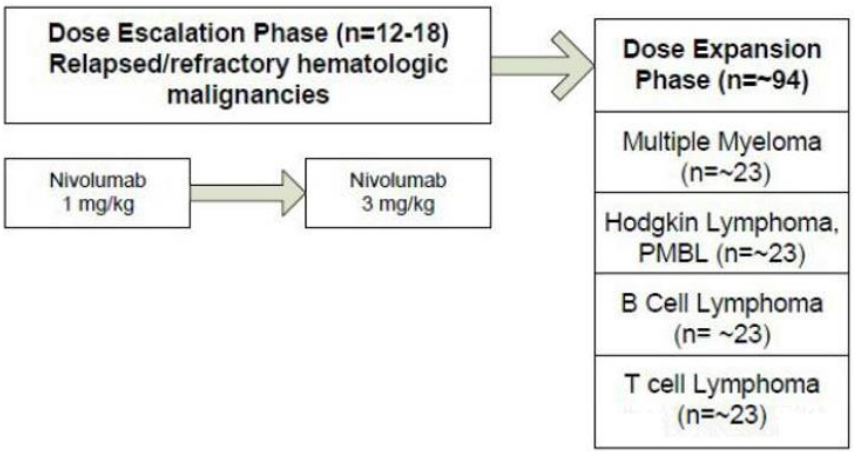
The study was conducted in three phases: screening (up to 28 days), treatment (up to 2 years), and follow-up (up to 12 months), with the possibility of retreatment and a subsequent follow-up (70 days). All patients underwent CT and FDG-PET at screening. The first dose administered followed by a 3-week period for pharmacokinetic and pharmacodynamics assessments of nivolumab. A response assessment following administration of the first dose was obtained, and the treatment was administered every two weeks thereafter. Patients were evaluated for efficacy at weeks 4, 8, 16, and 24 and every 16 weeks thereafter. CT and FDG-PET scanning were performed for confirmation of a complete response.[6]

Patients continued to receive study drug for up to two years or until confirmed CR, confirmed progressive disease or unacceptable toxicity. Patients who discontinued study treatment were followed for 100 days for safety data collection. Patients who had ongoing disease control (i.e., ongoing CR, PR or stable disease) entered the first follow-up period, during which patients were off the study drug but assessments were continued for one year. For the purpose of survival data collection, all patients were to be followed for five years after the initiation of study treatment, or until death, consent was withdrawn, lost to follow up, completion of the study.[6]

This study is ongoing. Two interim analyses were performed based on the data from 16-Jun-2014 [6] and 11-Aug-2015 clinical data database locks. Pharmacokinetic database lock was on 20-Aug-2015, and IRRC database lock was on 20-Oct-2015.

The original study protocol was published on 13-Mar-2012. The revised protocol incorporated 10 amendments.[5] The most relevant amendments to the study cohort of interest were as follows: on 21-Dec-2012, Amendment 02 eliminated the 10 mg/kg pre-determined dose level, and modified the discontinuation criteria to be more rigorous. On 15-Apr-2015, Amendment 10 allowed for the retrospective collection of radiographic images for blinded independent central review for nivolumab in cHL patients.[5]

Figure 6.3 CHECKMATE-039 Study Design



Source: [Checkpoint document][5]

b) Populations

CHECKMATE-205

As of October 2015 data cut-off, 240 patients were treated with nivolumab: (63 in Cohort A; 80 in Cohort B; and 97 in Cohort C).[3] Table 6.3 shows the baseline characteristics of the study participants. 126 (52.5%) were from Europe and 114(47.5%) were from the US and Canada. The median age of the patient population was 34 years (range 18 to 72), 76.7% of pts had stage III or IV disease at study entry 58.8% were male, 86.7% were white, 45.4% had an ECOG performance status of 1. The patients had received a median of four prior systemic cancer regimens (range 1 to 15), 53.8% had B-symptoms at the time of initial diagnosis, 41.3% had extra-lymphatic involvement at the baseline, and 67.1% had prior radiation therapy. The main differences between the study cohorts were related to: the lower proportion of patients with stage IV disease (at the study entry) in Cohort A (38.1%), when compared with Cohorts B (67.5%) and C (59.8%); the longer median time from initial diagnosis to the first dose of nivolumab in Cohort B (6.15 years), when compared with Cohort A (3.02 years) and Cohort C (3.41years); the longer median time from the most recent transplant to the first dose of nivolumab in Cohort B (3.37years), when compared with Cohorts A (1.03 years) ,and Cohort C (1.72 years); and the higher proportion of patients with a history ≥ 2 ASCTs in Cohort B (7.5%), when compared with Cohort A (1.6%) and Cohort C (0%). Furthermore, fewer patients in Cohort A had ≥4 prior lines of cancer therapy (20.7%), when compared with Cohort B (76.3%) and Cohort C (64.9%); and a higher proportion of patients in Cohort A had longer than a 6-month time gap between completion of the most recent prior regimen and the study treatment (77.8% versus 22.5% in Cohort B, and 36.1% in Cohort C).[3]

As of December 2016 data cut-off, 243 patients were included in the study (63 in Cohort A; 80 in Cohort B; and 100 in Cohort C). Of the 100 patients who were enrolled in Cohort C, 33 had received BV before, 58 after, and 9 both before and after ASCT.[2] The median age of the patient population was 34 years (range 18 to 72), 77.0% of pts had stage III or IV disease at study entry, 58.0% were male, and 46% had an ECOG performance status of 1. Patients had received a median

of four prior systemic cancer regimens (range; 2 to 15), and 67.1% had prior radiation therapy.[2] The main differences between the study cohorts were related to: the lower proportion of patients with stage IV disease (at the study entry) in Cohort A (38.0%), when compared with Cohorts B (68.0%) and C (56.0%); the longer median time from initial diagnosis to the first dose of nivolumab in Cohort B (6.2 years), when compared with Cohort A (3.1 years) and Cohort C (3.5 years); the longer median time from the most recent transplant to the first dose of nivolumab in Cohort B (3.4 years), when compared with Cohorts A (1.0 years) ,and Cohort C (1.7 years).[2]

Table 6.3 Baseline Characteristics of Patients in Cohorts A, B, and C from CHECKMATE-205 trial, 05-Oct-2015 data cut-off

	Cohort A N = 63	Cohort B N = 80	Cohort C N = 97	Cohort A+B+C N = 240
AGE				
N	63	80	97	240
MEAN	36.3	38.7	36.2	37.1
MEDIAN	33.0	37.0	32.0	34.0
MIN , MAX	18 , 65	18 , 72	19 , 69	18 , 72
STANDARD DEVIATION	12.54	13.00	12.47	12.67
AGE CATEGORIZATION (%)				
< 65	62 (98.4)	77 (96.3)	94 (96.9)	233 (97.1)
>= 65 AND < 75	1 (1.6)	3 (3.8)	3 (3.1)	7 (2.9)
>= 75 AND < 85	0	0	0	0
>= 85	0	0	0	0
>= 75	0	0	0	0
>= 65	1 (1.6)	3 (3.8)	3 (3.1)	7 (2.9)
< 30	25 (39.7)	27 (33.8)	36 (37.1)	88 (36.7)
>= 30 AND < 45	21 (33.3)	28 (35.0)	33 (34.0)	82 (34.2)
>= 45 AND < 60	12 (19.0)	18 (22.5)	25 (25.8)	55 (22.9)
>= 60	5 (7.9)	7 (8.8)	3 (3.1)	15 (6.3)
GENDER (%)				
MALE	34 (54.0)	51 (63.8)	56 (57.7)	141 (58.8)
FEMALE	29 (46.0)	29 (36.3)	41 (42.3)	99 (41.3)
RACE (%)				
WHITE	54 (85.7)	71 (88.8)	83 (85.6)	208 (86.7)
BLACK OR AFRICAN AMERICAN	2 (3.2)	4 (5.0)	6 (6.2)	12 (5.0)
ASIAN	3 (4.8)	1 (1.3)	5 (5.2)	9 (3.8)
AMERICAN INDIAN OR ALASKA NATIVE	0	0	2 (2.1)	2 (0.8)
NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDER	0	0	0	0
OTHER	4 (6.3)	4 (5.0)	1 (1.0)	9 (3.8)
ETHNICITY (%)				
HISPANIC OR LATINO	3 (4.8)	1 (1.3)	1 (1.0)	5 (2.1)
NOT HISPANIC OR LATINO	30 (47.6)	63 (78.8)	54 (55.7)	147 (61.3)
NOT REPORTED	30 (47.6)	16 (20.0)	42 (43.3)	88 (36.7)

	Number of Subjects (%)			
	Cohort A N = 63	Cohort B N = 80	Cohort C N = 97	Cohort A+B+C N = 240
PERFORMANCE STATUS (ECOG) [%]				
0	40 (63.5)	42 (52.5)	49 (50.5)	131 (54.6)
1	23 (36.5)	38 (47.5)	48 (49.5)	109 (45.4)
SMOKING STATUS				
CURRENT/FORMER	22 (34.9)	32 (40.0)	34 (35.1)	88 (36.7)
NEVER SMOKED	38 (60.3)	45 (56.3)	60 (61.9)	143 (59.6)
UNKNOWN	3 (4.8)	3 (3.8)	3 (3.1)	9 (3.8)
REGION				
US/CANADA	26 (41.3)	47 (58.8)	41 (42.3)	114 (47.5)
EUROPE	37 (58.7)	33 (41.3)	56 (57.7)	126 (52.5)
REST OF THE WORLD	0	0	0	0
DISEASE STAGE AT INITIAL DIAGNOSIS				
STAGE I	2 (3.2)	2 (2.5)	3 (3.1)	7 (2.9)
STAGE II	28 (44.4)	32 (40.0)	39 (40.2)	99 (41.3)
STAGE III	22 (34.9)	23 (28.8)	22 (22.7)	67 (27.9)
STAGE IV	10 (15.9)	22 (27.5)	31 (32.0)	63 (26.3)
NOT REPORTED	1 (1.6)	1 (1.3)	2 (2.1)	4 (1.7)
IPS AT INITIAL DIAGNOSIS				
0-2	19 (30.2)	18 (22.5)	13 (13.4)	50 (20.8)
>= 3	8 (12.7)	19 (23.8)	15 (15.5)	42 (17.5)
NOT REPORTED	36 (57.1)	43 (53.8)	69 (71.1)	148 (61.7)
DISEASE STAGE AT STUDY ENTRY				
STAGE I	1 (1.6)	1 (1.3)	2 (2.1)	4 (1.7)
STAGE II	20 (31.7)	11 (13.8)	20 (20.6)	51 (21.3)
STAGE III	17 (27.0)	14 (17.5)	17 (17.5)	48 (20.0)
STAGE IV	24 (38.1)	54 (67.5)	58 (59.8)	136 (56.7)
NOT REPORTED	1 (1.6)	0	0	1 (0.4)
B-SYMPTOMS AT INITIAL DIAGNOSIS				
PRESENT	34 (54.0)	46 (57.5)	49 (50.5)	129 (53.8)
ABSENT	28 (44.4)	34 (42.5)	42 (43.3)	104 (43.3)
NOT REPORTED	1 (1.6)	0	6 (6.2)	7 (2.9)
BULKY DISEASE AT BASELINE				
YES	10 (15.9)	17 (21.3)	21 (21.6)	48 (20.0)
NO	53 (84.1)	63 (78.8)	76 (78.4)	192 (80.0)

	Number of Subjects (%)			
	Cohort A N = 63	Cohort B N = 80	Cohort C N = 97	Cohort A+B+C N = 240
EXTRA LYMPHATIC INVOLVEMENT AT BASELINE				
YES	24 (38.1)	36 (45.0)	39 (40.2)	99 (41.3)
NO	39 (61.9)	44 (55.0)	58 (59.8)	141 (58.8)
BONE MARROW INVOLVEMENT AT BASELINE				
YES	3 (4.8)	8 (10.0)	7 (7.2)	18 (7.5)
NO	60 (95.2)	72 (90.0)	90 (92.8)	222 (92.5)
TIME FROM INITIAL DIAGNOSIS TO FIRST TRANSPLANT (YEARS)				
N	62	80	97	239
MEDIAN (MIN - MAX)	1.62 (0.6 - 24.5)	1.34 (0.1 - 15.7)	1.63 (0.5 - 14.5)	1.50 (0.1 - 24.5)
TIME FROM MOST RECENT TRANSPLANT TO FIRST DOSE OF STUDY THERAPY (YEARS)				
N	63	80	97	240
MEDIAN (MIN - MAX)	1.03 (0.3 - 18.2)	3.37 (0.2 - 19.0)	1.70 (0.2 - 17.0)	2.02 (0.2 - 19.0)
TIME FROM MOST RECENT TRANSPLANT TO FIRST SUBSEQUENT THERAPY (MONTHS)				
N	63	80	97	240
MEDIAN (MIN - MAX)	8.54 (0.0 - 136.9)	12.85 (0.0 - 159.0)	8.15 (0.0 - 200.9)	9.33 (0.0 - 200.9)
TIME FROM INITIAL DIAGNOSIS TO FIRST DOSE OF STUDY THERAPY (YEARS)				
N	62	80	97	239
MEDIAN (MIN - MAX)	3.02 (1.0 - 30.8)	6.15 (1.3 - 25.1)	3.41 (1.0 - 24.9)	4.43 (1.0 - 30.8)

Abbreviation: IPS = International Prognostic Score.

	Number of Subjects (%)			
	Cohort A N = 63	Cohort B N = 80	Cohort C N = 97	Cohort A+B+C N = 240
NUMBER OF PRIOR SYSTEMIC REGIMEN RECEIVED (A)				
1	2 (3.2)	0	0	2 (0.8)
2	29 (46.0)	0	6 (6.2)	35 (14.6)
3	19 (30.2)	19 (23.8)	28 (28.9)	66 (27.5)
4	10 (15.9)	22 (27.5)	33 (34.0)	65 (27.1)
>= 5	3 (4.8)	39 (48.8)	30 (30.9)	72 (30.0)
MEDIAN (MIN, MAX)	3 (1, 5)	4 (3, 15)	4 (2, 9)	4 (1, 15)
FIRST LINE REGIMEN				
ABVD	45 (71.4)	68 (85.0)	83 (85.6)	196 (81.7)
ESCALATED BEACOPP	1 (1.6)	0	2 (2.1)	3 (1.3)
OTHER	17 (27.0)	12 (15.0)	12 (12.4)	41 (17.1)
SECOND LINE REGIMEN				
ABVD	4 (6.3)	2 (2.5)	4 (4.1)	10 (4.2)
ESCALATED BEACOPP	2 (3.2)	2 (2.5)	2 (2.1)	6 (2.5)
DHAP	11 (17.5)	9 (11.3)	7 (7.2)	27 (11.3)
ESHAP	5 (7.9)	6 (7.5)	5 (5.2)	16 (6.7)
ICE	13 (20.6)	28 (35.0)	23 (23.7)	64 (26.7)
GVD	0	1 (1.3)	2 (2.1)	3 (1.3)
IGEV	2 (3.2)	8 (10.0)	18 (18.6)	28 (11.7)
OTHER	23 (36.5)	24 (30.0)	34 (35.1)	81 (33.8)
NUMBER OF PRIOR ASCT				
1	62 (98.4)	74 (92.5)	97 (100.0)	233 (97.1)
>= 2	1 (1.6)	6 (7.5)	0	7 (2.9)
TYPE OF ASCT PREPARATIVE REGIMEN RECEIVED FOR MOST RECENT PRIOR TRANSPLANT				
ANY PREPARATIVE REGIMEN	35 (55.6)	51 (63.8)	47 (48.5)	133 (55.4)
BEAM	15 (23.8)	22 (27.5)	15 (15.5)	52 (21.7)
CBV	3 (4.8)	5 (6.3)	4 (4.1)	12 (5.0)
SUBJECTS WITH OTHER PREPARATIVE REGIMEN	17 (27.0)	24 (30.0)	28 (28.9)	69 (28.8)
BEST RESPONSE TO REGIMEN PRIOR TO MOST RECENT ASCT				
CR OR PR	52 (82.5)	71 (88.8)	79 (81.4)	202 (84.2)
SD	5 (7.9)	3 (3.8)	8 (8.2)	16 (6.7)
RELAPSE/PD	5 (7.9)	4 (5.0)	8 (8.2)	17 (7.1)
UNABLE TO DETERMINE/NOT REPORTED	1 (1.6)	2 (2.5)	2 (2.1)	5 (2.1)
RESPONSE AT MOST RECENT ASCT				
CR OR PR	35 (55.6)	50 (62.5)	60 (61.9)	145 (60.4)
SD	5 (7.9)	6 (7.5)	8 (8.2)	19 (7.9)
RELAPSE/PD	7 (11.1)	4 (5.0)	16 (16.5)	27 (11.3)
UNABLE TO DETERMINE/NOT REPORTED	16 (25.4)	20 (25.0)	13 (13.4)	49 (20.4)
BEST REPOSNSE TO MOST RECENT ASCT				
CR OR PR	36 (57.1)	29 (36.3)	42 (43.3)	107 (44.6)
SD	2 (3.2)	6 (7.5)	3 (3.1)	11 (4.6)
RELAPSE/PD	20 (31.7)	37 (46.3)	43 (44.3)	100 (41.7)
UNABLE TO DETERMINE/NOT REPORTED	5 (7.9)	8 (10.0)	9 (9.3)	22 (9.2)
BEST RESPONSE TO REGIMEN POST MOST RECENT ASCT				
CR OR PR	6 (9.5)	37 (46.3)	31 (32.0)	74 (30.8)
SD	1 (1.6)	10 (12.5)	11 (11.3)	22 (9.2)
RELAPSE/PD	2 (3.2)	25 (31.3)	28 (28.9)	55 (22.9)
UNABLE TO DETERMINE/NOT REPORTED	54 (85.7)	8 (10.0)	27 (27.8)	89 (37.1)
TIME FROM COMPLETION OF MOST RECENT PRIOR REGIMEN TO TREATMENT				
< 3 MONTHS	7 (11.1)	44 (55.0)	46 (47.4)	97 (40.4)
3-6 MONTHS	7 (11.1)	18 (22.5)	16 (16.5)	41 (17.1)
> 6 MONTHS	49 (77.8)	18 (22.5)	35 (36.1)	102 (42.5)
PRIOR SURGERY RELATED TO CANCER				
YES	34 (54.0)	46 (57.5)	41 (42.3)	121 (50.4)
NO	29 (46.0)	34 (42.5)	56 (57.7)	119 (49.6)
PRIOR RADIOTHERAPY				
YES	36 (57.1)	59 (73.8)	66 (68.0)	161 (67.1)
NO	27 (42.9)	21 (26.3)	31 (32.0)	79 (32.9)

Source: [EPAR 2015; pages 26-28] [3]

CHECKMATE-039

The baseline characteristic s of the CHECKMATE-039 study participants are shown in Table 6.4. As the table shows, the median age of the study participants was 35 years (range 20 to 54 years).The majority of all cHL patients were white 20 (87%), and had a baseline ECOG performance-status score of 1 (74%). There were 12 (52%) male and 11 (48%) female included in the study. All the

patients had been heavily pre-treated, and 65% of them had received four or more previous systemic treatments. Of the 23 patients, 78% had undergone ASCT; 78% had a history of treatment with BV therapy; and 83% had received radiation therapy. Extra-nodal disease involving bone, lung, pelvis, peritoneum, or pleura was reported in 17% of the patients.[6] The most common site of lesions other than lymph nodes were lung (34.8%) and other sites included liver (13.0%) and kidney (4.3%). None of the patients had central nervous system disease.[3] Except one patient who presented with mixed cellularity histologic findings at the baseline, all other patients had the nodular sclerosis type of Hodgkin lymphoma. The most common first-line chemotherapy was ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine), which was administered in 20 out of 23 patients (87%).[6]

Among the 23 study participants, 15 patients had a history of prior BV treatment as a salvage therapy after failure of ASCT. Of the remaining eight patients, five were ASCT-naive, two had failed on ASCT but were BV- naive, and one had failed on BV followed by ASCT.[5]

Table 6.4 - Baseline Characteristics of Patients in CHECKMATE-039 trial

Characteristic	Value
Age — yr	
Median	35
Range	20–54
Male sex — no. (%)	12 (52)
Race — no. (%)*	
White	20 (87)
Black	2 (9)
Other	1 (4)
ECOG performance-status score — no. (%)†	
0	6 (26)
1	17 (74)
Histologic findings — no. (%)	
Nodular sclerosis	22 (96)
Mixed cellularity	1 (4)
No. of previous systemic therapies — no. (%)	
2 or 3	8 (35)
4 or 5	7 (30)
≥6	8 (35)
Previous treatment — no. (%)	
Brentuximab vedotin	18 (78)
Autologous stem-cell transplantation	18 (78)
Radiotherapy	19 (83)
Extranodal involvement — no. (%)‡	4 (17)

* Race was either self-reported or reported by investigators.
† Eastern Cooperative Oncology Group (ECOG) scores indicate the performance status of patients with respect to activities of daily living on a scale from 0 to 5, with higher numbers indicating greater disability. A score of 0 indicates that the patient is fully active and able to carry out all predisease activities without restriction, and a score of 1 indicates that the patient is restricted in physically strenuous activity but is ambulatory and able to carry out work of a light nature.
‡ Sites of extranodal disease were bone, lung, pelvis, peritoneum, and pleura.

Source: From The New England Journal of Medicine, Stephen M. Ansell, Alexander M. Lesokhin, Ivan Borrello, et al, PD-1 Blockade with Nivolumab in Relapsed or Refractory Hodgkin's Lymphoma, Volume No. 372, Page No 324. Copyright © (2018) Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.[6]

c) Interventions

CHECKMATE-205

Treatment Dosing Schedule

Nivolumab was administered to all patients, through IV infusions, at 3 mg/kg patient's body weight over 60 minutes, on the first day of each 14-day cycle. The minimum permitted interval between the doses was 12 days and the injections had to be administered no more than three days after the scheduled dosing date.[3]

Dose delays, reductions or modifications

CHECKMATE-205 did not allow for dose reductions or escalations. However, Dose delays of less than 6 weeks were permitted for all drug-related adverse events (AEs) according to pre-specified criteria.

Concomitant interventions

Corticosteroids were permitted in topical, ocular, intra-articular, intranasal, and inhalational forms, and for the purposes of prophylaxis or treatment of AEs or non-autoimmune conditions. The following medications were prohibited during the study: immune-suppressive agents, except for the treatment of drug-related AEs; systemic corticosteroids >10 mg daily prednisone equivalent; any concurrent antineoplastic therapy, including chemotherapy, hormonal therapy, immunotherapy, radiation therapy (except for palliative radiation therapy), and standard or investigational agents used for treatment of cancer.[3]

CHECKMATE-039

Treatment Dosing Schedule

Nivolumab was administered to all 23 patients, through IV infusions, at 3 mg/kg patient's body weight Patients received nivolumab at week one, week four and every two weeks until disease progression or complete response or for a maximum of two years.[6]

Dose delays, reductions or modifications

Dose reductions and escalations were not permitted. Dose delays of less than 28 days were permitted according to pre-specified criteria. Patients with treatment delays of 28 days or longer would discontinue treatment and enter the follow-up period with the exception of delays related to prophylactic vaccinations.[3]

Concomitant interventions

Corticosteroids were permitted in topical, ocular, intra-articular, intranasal, and inhalational forms, and for the purposes of prophylaxis or treatment of AEs or non-autoimmune conditions. While on therapy, patients could be vaccinated with the inactivated seasonal influenza vaccine without restriction. Influenza vaccines containing live virus or other clinically indicated vaccinations for infectious diseases (i.e., pneumovax, varicella, etc.) might also be administered after taking necessary precautions (e.g., required study drug washout period prior to and after administration of the vaccine. The following medications were prohibited during the study: Concurrent chemotherapy, hormonal therapy or immunotherapy regimens, systemic corticosteroids within 7 days of study entry, concurrent immunosuppressive agents, concurrent use of denosumab, vaccines except as noted above.[6]

d) Patient Disposition

CHECKMATE-205

The patient disposition for the CHECKMATE-205 trial is presented in Figure 6.4.The trial enrolled patients in Cohorts A, B, and C between 26-Aug-2014 and 03-Sep-2015.[3] Of the 276 subjects who were enrolled in the study, 243(88.0%) were treated with nivolumab (63 in Cohort A; 80 in Cohort B; and 100 in Cohort C). The most common reason for not being treated was that patients no longer met the study eligibility criteria (25 patients; 9.1%), followed by adverse events (4; patients; 1.5%), and consent withdrawal (2 patients; 0.7%). One patient died before receiving the study treatment, and one patient had poor compliance with the study treatment.[CA209205-csr;

Consort diagram][38] There were two major protocol deviations in CHECKMATE-205 trial, which resulted from concurrent chemotherapy in two (0.8%) of the patients.[5]

As of October 2015 data cut-off (after a median follow up duration 8.9 months (IQR 7.8, 9.9)), 195 out of 240 (81.3%) participants (85.7% of patients in Cohort A, 63.8% in Cohort B, and 92.8% in Cohort C) continued on treatment. The main reasons for discontinuation were disease progression (16%), study drug toxicity (5%), patient's request to withdraw (3%), lost to follow up (1%), and other reasons (10%; including stem-cell transplantation and lack of response to the study treatment).[1,3]

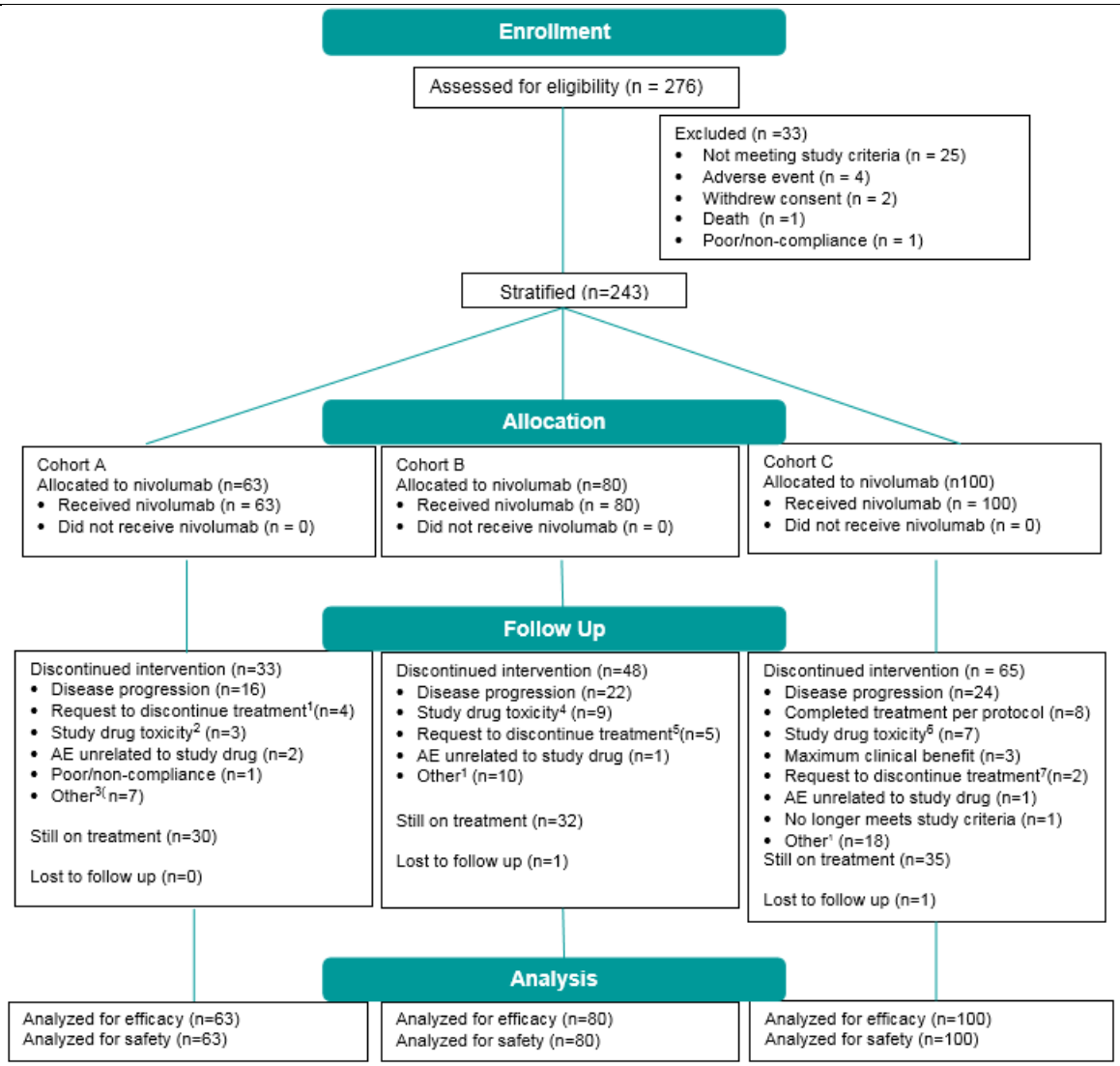
As of December 2016 data cut-off (after median follow-up periods of 19, 23, and 16 months for Cohorts A, B, and C, respectively),[2] 97 (40.0%) of 243 participants (48% of patients in Cohort A, 40.0% in Cohort B, and 35.0% in Cohort C) continued on treatment. The main reasons for discontinuation included: disease progression (26%), study drug toxicity (8%), adverse events unrelated to the study drug (2%), achieving maximum clinical benefit (1%), complete treatment (3%), stem-cell transplantation (12%), or other reasons (21%).[2] The patient disposition for the CHECKMATE-205 trial is presented in Figure 6.4.[CA209205-csr; Consort diagram][38]

CHECKEMATE-039

The patient disposition for the CHECKMATE-039 trial is presented in Figure 6.5. As the figure shows, a total of 23 patients with relapsed or refractory cHL were enrolled in the study including 15 patients in whom previous ASCT and BV had failed, 5 patients who had failed on BV but had not undergone ASCT before BV, and 3 patients who were BV-naive.

As of 11-Aug-2015 data cut-off date, 20 (87%) of 23 patients had discontinued treatment for the following reasons of: disease progression (6 patients; 26.1%), study drug toxicity (2 patients; 8.7%), patient's request (one patient; 4.3%), and other, including stem cell transplants (5 patients; 21.7%). The study treatment was discontinued in four patients (17.4%) due to a complete response, and in two patients (8.7%) due to the completion of 2 years of therapy. A total of three patients were continuing treatment with partial response to the study treatment [CA209039 interim CSR, pages 68 and 79][39] In CHECKMATE-039, there were two major protocol deviations which resulted from failure to obtain informed consent in one case and failure to perform a baseline laboratory test in a second case.[5]

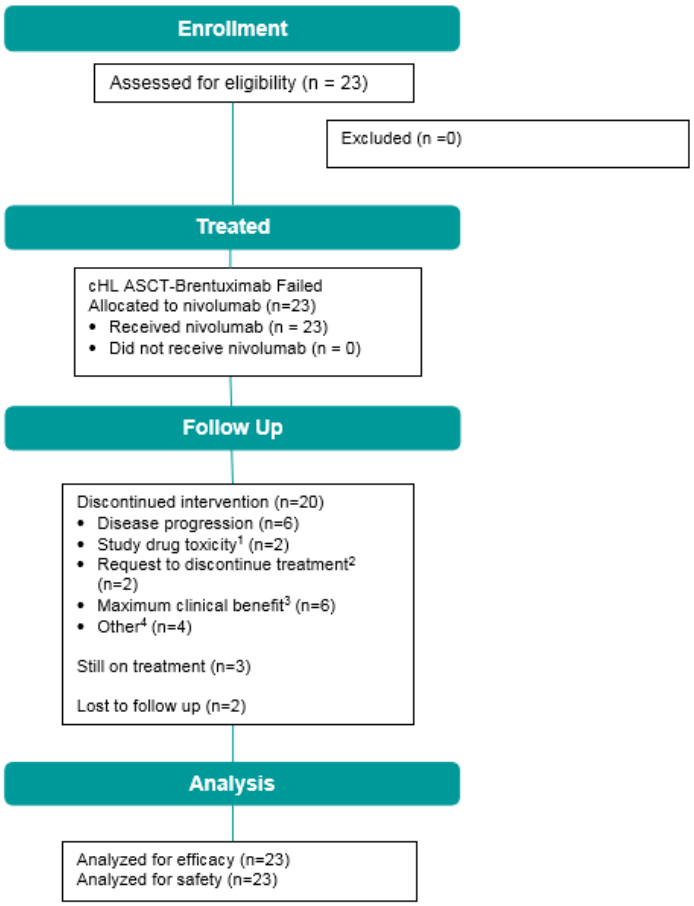
Figure 6.4 Consort Diagram of study participants in CHECKMATE-205, December 2016 data cut-off



[1] Cohort A subjects withdrew consent: 1) due to good condition, the patient did not want further treatment, 2) patient decided to continue to receive nivolumab locally off-label, 3)patient decided to receive nivolumab at referring physician's office, of protocol, 4) refusal of nivolumab against medical advice
[2] Cohort A study drug toxicity: hepatitis, syncope, organising pneumonia
[3] 30 of the 35 patients that specified "other" as the reason to discontinue treatment, "transplant" was further specified as the reason for discontinuation.
[4] Cohort B study drug toxicity: autoimmune hepatitis, pneumonitis, aspartate aminotransferase increase, eye pruritus, rhinitis, alanine aminotransferase increase
[5] Cohort B subjects withdrew consent: 1) site investigator and patient decided to discontinue treatment, 2) patient transferred to France and continued in a named patient program, 3) patient had comorbidities and felt it was in their best interest to focus on those issues, 4) subject receiving (non-study drug) nivolumab locally, 5) subject's arthralgia and restrictive schedule.
[6] Cohort C study drug toxicity: pneumonitis, pleural effusion, autoimmune hepatitis, hyperbilirubinaemia, pericardical effusion, diarrhoea, pneumonia, autoimmune nephritis, gamma-glutamyltransferase increased
[7] Cohort C subjects withdrew consent: 1) patient did not wish to return to the study site for treatment and 2) subject received approval to receive commercial nivolumab through their insurance closer to home.

Source: [CA209205-csr][38]

Figure 6.5 CONSORT diagram of participants in CHECKMATE-039, August 2015 data cut-off



[1] Study drug toxicity: pancreatitis, myelodysplastic syndrome
[2] Subject request: transplant, joint and muscle pain
[3] Maximum clinical benefit: achieved a CR or completed 2 years of therapy
[4] Other: transplant

Source: [CA209039 Interim csr][39]

e) Limitations/Sources of Bias

- CHECKMATE-039 is a phase 1 open-label single arm study primarily designed to assess the safety and tolerability profile of nivolumab in the treatment of refractory hematologic malignancies, including cHL. Therefore, it is difficult to make a conclusion on the efficacy of nivolumab based on the data obtained from this study.
- CHECKMATE-205 is a non-comparative open-label study with no active treatment or placebo control groups. Randomized comparisons between the study treatment (nivolumab) and its potential comparators are needed to justify the observed clinical efficacy and safety outcomes. Although nivolumab resulted in clinical and survival benefits, no conclusions could be made regarding the efficacy of this drug relative to currently used treatment options for patients with refractory cHL.

- The open label nature of the trials might introduce the risk of reporting and performance biases, as the study participants and the investigators were aware of the treatment assignments. This could particularly be important in reporting of subjective outcomes (e.g., AEs) by the patients and care providers. In open-label trials, the reporting behavior of patients may be influenced by their information about the new drug and its side effects. The investigators and assessors may measure and report the AEs of the new drug more frequently and consider the AEs of the comparators as normal or acceptable, or vice versa. To decrease the impact of this bias, the investigators used an independent review committee (IRRC) to assess the primary and secondary outcomes of the study (including ORR, CR, PR, and DOR). However, it is not clear if the members of the IRRC were blinded to the treatment history of the study participants. In addition, subjective outcomes (i.e. AEs and QoL) may also be biased as a result of the open-label design.
- Both trials are ongoing (not recruiting) and, therefore, the duration of follow up for a proportion of patients might not be long enough to make an inference on the observed survival benefits.
- In CHECKMATE-205, ORR was the primary endpoint. PFS, OS, and health-related QoL endpoints were exploratory outcomes. Therefore the trial might not have been sufficiently powered to reliably estimate survival rates or quality of life outcomes.

6.3.2.1 Detailed Outcome Data and Summary of Outcomes

Efficacy Outcomes

CHECKMATE-205

Younes et al (2016) published the results of the primary analysis after the pre-specified minimum follow-up period of 6 months was met for Cohort B (05-Oct-2015 data cut-off), which represents a median duration of follow up of 8.9 months (IQR 7.8 to 9.9 months).[1] Data from April 2016 and June-2016 data cut-off dates were published by the European Medicines Agency (OPDIVO assessment report; October 2016)[3] Longer term follow up results (16-Dec-2016 data cut-off), from cohorts A, B, and C, were presented at the 14th International Conference on Malignant Lymphoma in June 2017 and published in the form of a conference abstract. As of December 2016 data cut-off, the median follow-up time periods were 19, 23, and 16 months for Cohorts A, B, and c, respectively.[2] The main efficacy outcomes for this study are summarized below.

Objective Response Rate and Best Overall response

The primary outcome of the trial was ORR as assessed by IRRC, and defined as the percentage of treated patients with a best overall response of complete or partial remission, as per the revised IWG criteria for Malignant Lymphoma (2007 criteria). Best overall response was defined as the best response between the first dose and progression or subsequent therapy, whichever occurred first. ORR was estimated using a binomial response rate and its corresponding two-sided 95% exact confidence intervals (CIs) using Clopper-Pearson method. The null hypothesis was rejected if the 2-sided 95% CI lower bound was greater than 20%. IRRC-assessed and investigator assessed CR rates were estimated using a binomial response rate and its corresponding two-sided 95% exact CIs, using Clopper-Pearson method.[3]

As of October 2015 data cut-off date (Cohort B; Table 6.5):[1]

- The IRRC-assessed ORR was achieved in 53 out of 80 patients (66.3%, 95% CI 54.8–76.4).
- The best overall responses included complete remission in seven (9%) patients and partial remission in 46 (58%) patients.

- The investigator-assessed objective response was achieved in 58 out of 80 patients (72.5%, 95% CI 61.4–81.9)
- The best overall responses included complete remission in 22 (28%) patients and partial remission in 36 (45%) patients.
- Concordance between IRRC and investigator-assessments was 76.3% and 53.8% for ORR and best overall response rate, respectively.
- The median time to first objective response (IRRC-assessed) was 2.1 months (IQR 1.9–3.0).

A post-hoc analysis of medical record data showed that 31 out of 43 (72%) patients, who had no previous response to the most recent BV treatment before trial recruitment, achieved IRRC-assessed objective response after nivolumab treatment.[1]

As of December 2016 data cut-off date (Cohorts A, B, and C; Table 6.6):[2]

- ORR was achieved in 65% of patients in Cohort A, 68% of patients in Cohort B, and 73% of patients in Cohort C
- CR was achieved in 29%, 13%, and 12% of patients in Cohorts A, B, and C, respectively

Table 6.5 Objective and Best Overall Response Rates in Cohort B (05-Oct-2015 data cut-off)

	IRRC assessed (n=80)	Investigator assessed (n=80)
Objective response	53 (66·3%; 95% CI 54·8–76·4)	58 (72·5%; 95% CI 61·4–81·9)
Best overall response		
Complete remission	7 (9%)	22 (28%)
Partial remission	46 (58%)	36 (45%)
Stable disease	18 (23%)	18 (23%)
Progressive disease	6 (8%)	3 (4%)
Unable to determine	3 (4%)*	1 (1%)†

Data are n (%), unless specified otherwise. *Two patients had no post-baseline tumour assessment available before or on the day of subsequent therapy (if any); for one patient, all post-baseline tumour assessments before or on the day of subsequent therapy (if any) were unknown. †No radiographic assessment was done after the first dose of nivolumab.

Source: Reprinted from The Lancet Oncology, Vol. 17 number 9, Younes A, Santoro A, Shipp M, et al., Nivolumab for classical Hodgkin's lymphoma after failure of both autologous stem-cell transplantation and brentuximab vedotin: a multicentre, multicohort, single-arm phase 2 trial, Page No. 1288, Copyright (2016), with permission from Elsevier.[1]

Table 6.6 - Objective and Best Overall Response Rates in Cohorts A, B, and C (December-2016 data cut-off)

	BV naïve (Cohort A) n = 63	BV after auto-HSCT (Cohort B) n = 80	BV before and/or after auto-HSCT (Cohort C) n = 100	Overall N = 243
Objective response per IRC,[a] % (95% CI)	**65 (52, 77)**	**68 (56, 78)**	**73 (63, 81)**	**69 (63, 75)**
Best overall response per IRC, %				
Complete remission[b]	29	13	12	16
Partial remission	37	55	61	53
Stable disease	24	21	15	19
Progressive disease	11	8	10	9
Unable to determine	0	4	2	2

BV = brentuximab vedotin; **CI** = confidence interval; **HSCT** = hematopoietic stem cell transplant; **IRC** = independent review committee

[a]Defined according to 2007 International Working Group Criteria
[b]All complete remissions confirmed by FDG-PET scan

Source: Fanale M, Engert A, Younes A, Armand P, Ansell S, Zinzani PL, et al. Nivolumab for relapsed/refractory classical Hodgkin lymphoma after autologous transplant: full results after extended follow-up of the phase 2 checkmate 205 trial [abstract]. Hematological oncology. 2017;Conference: 14th international conference on malignant lymphoma palazzo dei congressi. Switzerland. 35(Suppl 2):135-6.[2] Slide Presentation provided by Bristol-Myers Squibb

Duration of Response

Duration of response (DOR) was a secondary outcome in CHECKMATE-205 trial, and was defined as the time from first response (CR or PR) to the date of the first documented IRRC-assessed tumour progression, or death due to any cause, whichever occurred first. For patients who neither progressed nor died, the DOR was censored on the date of the patient's last evaluable tumor assessment. This endpoint was only evaluated in patients with a best objective response of CR or PR. The durations of CR and PR were only evaluated in subjects with best objective responses of CR and PR, respectively. The duration of CR (or PR) was defined as the time from first documentation of CR (or PR) to the date of initial objectively documented progression as determined using the 2007 IWG criteria or death due to any cause, whichever occurred first. Censoring was applied as per DOR definition. DOR, duration of CR, and duration of PR were estimated using the Kaplan-Meier product-limit method.[38]

As of 05-Oct-2015 data cut-off date (Cohort B).[1]

- The median duration of IRRC-assessed objective response was 7.8 months (95% CI 6.6 – not reached). The post-hoc analysis of the 43 patients, who had no previous response to the most recent BV treatment before trial recruitment, showed that 31 (72%) of the patients achieved IRRC-assessed objective response after the study treatment.
- The median investigator-assessed duration of objective response was 9.1 months (95% CI 6.74–not available). However, Younes et al. noted that this was an unstable estimate due to early censoring (37 of 58 responders who were still on treatment were censored prior to the median) and might change with additional follow-up.

- The median duration of investigator-assessed CR was 8.7 months (95% CI not available). Sixteen (72%) out of 22 patients with a CR were still continuing in response at the time of analysis.
- The median duration of investigator-assessed PR was 7.8 months (95% CI 6.7 – 7.8). Twenty two (61%) out of 36 patients with a CR were still continuing in response at the time of analysis.

As of 16-Dec-2016 data cut-off date (Cohorts A, B, and C; Table 6.7):[2]

- The median duration of IRRC-assessed objective response reached 20 months (95% CI 13 – 20) in Cohort A, 16 months (95% CI 8 – 20) in Cohort B, and 15 months (95% CI 9 – 17) in Cohort C.
- Overall the durations of response was 20 months (95% CI 16- not available) in patients with a CR, and 13 months (95% CI 9- 17) in patients with a PR.

Figure 6.6 provides more details on the DOR by best overall response (CR and PR) in all 243 treated patients in CheckMate205 trial.[2]

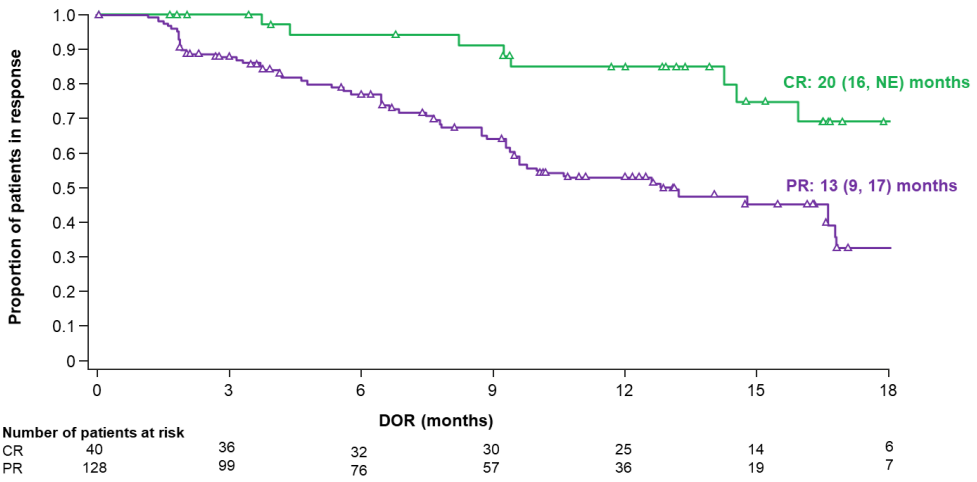
Table 6.7- Median Duration of Objective Response by Cohort in CHECKMATE-205 (December-2016 data cut-off date)

DOR by cohort	Cohort A n = 63	Cohort B n = 80	Cohort C n = 100	Overall N = 243
Median DOR in all responders, months	20 (13, 20)	16 (8, 20)	15 (9, 17)	17 (13, 20)
Median DOR in CR patients, months	20 (NE, NE)	20 (4, NE)	15 (8, NE)	20 (16, NE)
Median DOR in PR patients, months	17 (9, NE)	11 (7, 18)	13 (9, 17)	13 (9, 17)

All values are medians (95% CI); NE = not evaluable

Source: Fanale M, Engert A, Younes A, Armand P, Ansell S, Zinzani PL, et al. Nivolumab for relapsed/refractory classical Hodgkin lymphoma after autologous transplant: full results after extended follow-up of the phase 2 checkmate 205 trial [abstract]. Hematological oncology. 2017;Conference: 14th international conference on malignant lymphoma palazzo dei congressi. Switzerland. 35(Suppl 2):135-6.[2] Slide Presentation provided by Bristol-Myers Squibb

Figure 6.6- Duration of Objective Response by Best Overall Response in CHECKMATE-205 (December-2016 data cut-off date)



Source: Fanale M, Engert A, Younes A, Armand P, Ansell S, Zinzani PL, et al. Nivolumab for relapsed/refractory classical Hodgkin lymphoma after autologous transplant: full results after extended follow-up of the phase 2 checkmate 205 trial [abstract]. Hematological oncology. 2017;Conference: 14th international conference on malignant lymphoma palazzo dei congressi. Switzerland. 35(Suppl 2):135-6.[2] Slide Presentation provided by Bristol-Myers Squibb

Progression-Free Survival

PFS was an exploratory outcome in this study, and was defined as the time from the first dosing date to the date of the first documented tumor progression (as determined by the investigator using 2007 IWG criteria) or death due to any cause, whichever occurred first. Patients who died without a reported prior progression were considered to have progressed on the date of their death. Patients who did not progress or die were censored on the date of their last evaluable tumor assessment. Patients who did not have any tumor assessments, during the study follow up, and did not die were censored on the date they were randomized. Patients who received any subsequent anticancer therapy without a reported progression were censored at the last evaluable tumor assessment, prior to or on the date of starting their subsequent anti-cancer treatment.[38]

As of 05-Oct-2015 data cut-off date (Cohort B):

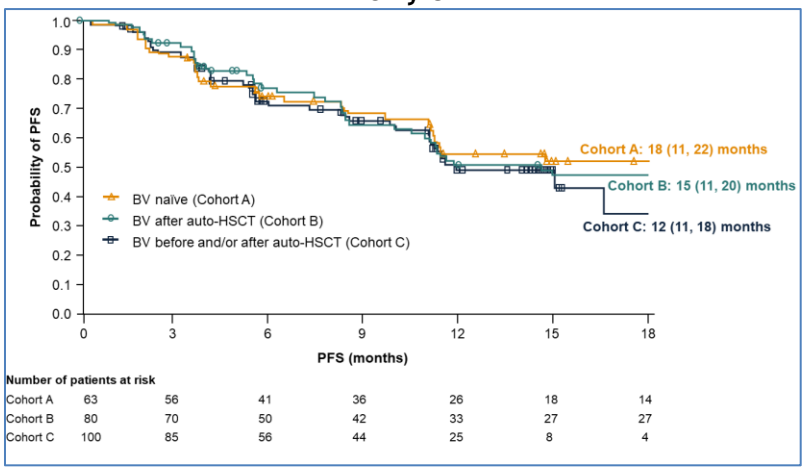
- With a minimum 6-month follow up period, IRRC-assessed PFS was 76.9% (95% CI 64.9–85.3), and IRRC-assessed overall survival was 98.7% (91.0–99.8).[1]
- Updated data from this cohort showed that at 12 months, 24 events (23 progression and one death) had occurred, and median PFS was 10.0 months (95% CI 8.41–not reached).[3]

As of 16-Dec-2016 data cut-off date (Cohorts A, B, and C):

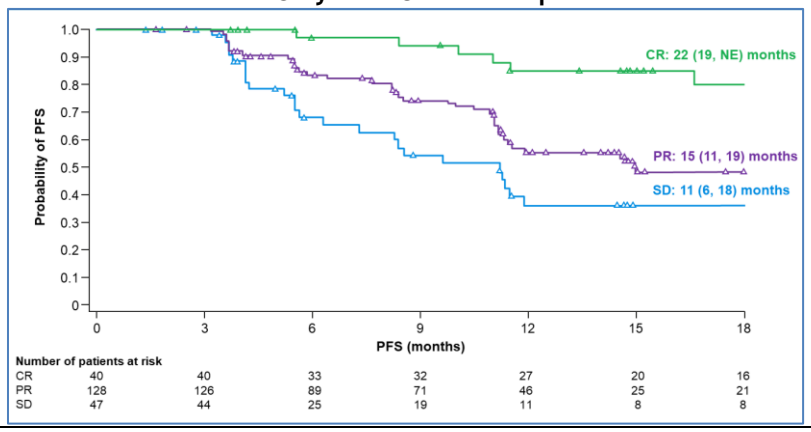
- The median IRRC-assessed PFS rates were:
  - 18.0 months (95% CI 11 - 22) in cohort A (22.24 months in patients with a CR, and 18.83 months in patients with a PR);
  - 15 months (95% CI 11 - 20) in cohort B (22.11 months in patients with a CR, and 14.65 months in patients with a PR; and
  - 11.93 months (95% CI 11.07 – 18.40) in Cohort C (16.59 months in patients with a CR, and 15.05 months in patients with a PR).[38]
- The PFS rate was 54.8% in Cohort A (at 12 months), 47.4% in Cohort B (at 18 months), and 49.1% in Cohort C (at 12 months) (Figure 6.7a).[2]
- Figure 6.7b illustrates the Kaplan-Meier curves for PFS in CHECKMATE-205 participants, based on the status of their overall response.

Figure 6.7- Progression-Free Survival in CHECKMATE-205 Trial (December-2016 data cut-off)

#a- PFS by Cohort



#b- PFS by Best Overall Response



Source: Fanale M, Engert A, Younes A, Armand P, Ansell S, Zinzani PL, et al. Nivolumab for relapsed/refractory classical Hodgkin lymphoma after autologous transplant: full results after extended follow-up of the phase 2 checkmate 205 trial [abstract]. Hematological oncology. 2017;Conference: 14th international conference on malignant lymphoma palazzo dei congressi. Switzerland. 35(Suppl 2):135-6.[2] Slide Presentation provided by Bristol-Myers Squibb

Overall Survival

OS was an exploratory outcome in this study, and was defined as the time from first dosing date to the date of death. For patients without documentation of death, OS was censored on the last date the subject was known to have been alive.[3]

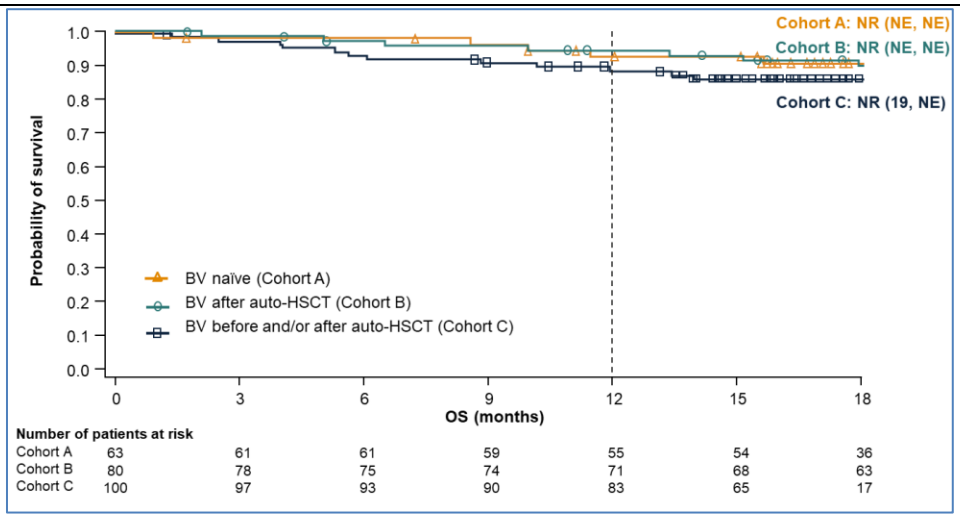
As of 16-Dec-2016 data cut-off date, median OS was not reached in none of the study cohorts.[2,3]

- After a minimum follow-up of 15 months (median follow-up 19.12 months), the OS rate was 93.4% in Cohort A
- After a minimum follow-up of 20 months (median follow-up 22.70 months), the OS rate was 89.2% in Cohort B

- After a minimum follow-up of 14 months (median follow-up 16.16 months), the OS rate was 88.7% in Cohort C

Figure 6.8 demonstrates the Kaplan-Meier OS curves for CHECKMATE-205 study cohorts.

Figure 6.8 - Overall Survival in CHECKMATE 205 Trial (December-2016 data cut-off)



Source: Fanale M, Engert A, Younes A, Armand P, Ansell S, Zinzani PL, et al. Nivolumab for relapsed/refractory classical Hodgkin lymphoma after autologous transplant: full results after extended follow-up of the phase 2 checkmate 205 trial [abstract]. Hematological oncology. 2017;Conference: 14th international conference on malignant lymphoma palazzo dei congressi. Switzerland. 35(Suppl 2):135-6.[2] Slide Presentation provided by Bristol-Myers Squibb

CHECKMATE-039

Ansell et al.[6] reported the safety and efficacy results for all 23 cHL patients who were enrolled in CHECKMATE-039 trial. Data for the subgroup of patients who had failed on ASCT and BV (n=15) was presented in the Americal Society of Hematilogi (ASH) 57th Annual Meeting,[7] and is published as part of the European Medicines Agency's assessment report for nivolumab in patients with Hodgkin lymphoma (October 2016).[3]

Objective Response Rate and Best Overall response

Investigator-assessed ORR was a primary outcome in CHECKMATE-039 trial, and IRRC-assessed ORR was a secondary outcome. ORR was defined as the total number of subjects whose best objective response was either a CR or PR divided by the total number of treated subjects. Two-sided 95% CIs for ORR, CR, and PR were estimated using Clopper-Pearson method.[6]

As of the 16-Jun-2014 data cut-off date (after a median follow-up of 40 weeks), the investigator-assessed ORR was achieved in 87% (95% CI: 66–97%) of 23 patients, with a CR in 4 patients (17%), a PR in 16 patients (70%), and stable disease in 3 patients (13%). Among the patients who received nivolumab following a disease recurrence post-ASCT and BV (n=15), the investigator-assessed ORR was 87% (95% CI: 60–98), with a CR in 1 patient (7%), a PR in 12 patients (80%), and stable disease in 2 patients (13%). Among the patients who never received BV, three patients had a CR, one had a PR and one had a stable disease.[6]

As of the 11-Aug-2015 data cut-off date (after a median follow-up of 86 weeks), ORR was reported in 20/23 (87%) of the patients; among those, 22% had a CR and 65% had a PR (Table 6.8).[3]

Duration of response

DOR was a secondary outcome in CHECKMATE-039 trial, and was defined as the time between the date of the first response and the date of first progression or the date of death. DOR, duration of CR, and duration of PR were analyzed using Kaplan-Meier method for patients who achieved CR or PR. The median DOR along with its 95% CI was provided using log-log transformation for constructing the CIs (Brookmeyer and Crowley method). The percentage of responders still in response at different time points (e.g., 3, 6, 12, 18 and 24 months) was presented based on the DOR Kaplan-Meier curve.[39]

As of the 11-Aug-2015 data cut-off date, the median DOR had not been reached (Table 6.8). The proportion of patients who continued on treatment at 1 year and 1.5 year follow-ups were 35% and 30%, respectively.[3]

Time to response

The time to a response (TTR) was a secondary outcome in CHECKMATE-039 trial, and was defined as the time from the date of the first dose to the date of the first response.

As of 16-Jun-2014 data cut-off date, 60% (12/20) of patients who had a CR or PR, had the first response by 8 (range: 3 to 39) weeks.[6]

As of 11-Aug-2015 data cut-off date, the investigator-assessed median TTR was 1.7 (range 0.7 to 8.9) months for all cHL patients, with time to CR being 5.3 (range 1.6 to 19.9) months, and time to PR 1.7 (range 0.7 to 8.9) months (Table 6.8). The majority of responses occurred within the first 3 months (83.3% (15/18) total responders). Seven out of 18 responders (38.9%) had an ongoing response at the time of the data cut-off.[3,39]

Progression-free survival

PFS was a secondary outcome in CHECKMATE-039 trial, and was defined as the time from the date of the first dose of study medication to the date of first disease progression or the date of death, whichever occurs first. Patients who died without a reported prior progression were considered to have progressed on the date of their death. Patients who did not progress or die were censored on the date of their last tumor assessment. Patients who did not have any on study tumor assessments were censored on the date they were assigned to receive the study treatment. PFS was estimated with the use of Kaplan– Meier methods.[6]

At 24 weeks (16-Jun-2014 data cut-off) the PFS was 86% (95%CI: 62–95).[6] Median PFS had not been reached at the 11-Aug-2015 data cut-off date [3,7]

Overall Survival

OS was an exploratory outcome in CHECKMATE039 trial, and was defined as the time between the date of first dose of study therapy and death. Patients who did not have a reported death were censored at the last known alive date. OS curve was generated by Kaplan-Meier method, and OS rates at Years 1 and 1.5 were estimated using the Kaplan-Meier curve.[6]

As of the 11-Aug-2015 data cut-off date, the median OS had not been reached.[3,7] OS rates at 1 year and 1.5 year were 91% (95% CI 69.5 to 97.8) and 83% (95% CI 60.1 to 93.1), respectively.[3]

Table 6.8 - Summary of efficacy results for cHL patients receiving nivolumab monotherapy in CHECKMATE-039 trial

	Number of Subjects (%)					
Efficacy Parameters	**IRRC Total Subjects (n=23)**	**Investigator Total Subjects (n=23)**	**IRRC ASCT-Bren Failed (n=15)**	**Investigator ASCT-Bren Failed (n=15)**	**IRRC cHL Other (n=8)**	**Investigator cHL Other (n=8)**
ORR	14 (61)	20 (87)	9 (60)	13 (87)	5 (63)	7 (88)
CR	3 (13)	5 (22)	0	2 (13)	3 (38)	3 (38)
PR	11 (48)	15 (65)	9 (60)	11 (73)	2 (25)	4 (50)
SD	7 (30)	3 (13)	5 (33)	2 (13)	2 (25)	1 (13)
Objective Response Achieved						
Within 9 weeks	13 (57)	11 (48)	8 (53)	8 (53)	5 (63)	3 (38)
Within 4 months	13 (57)	16 (70)	8 (53)	11(73)	5 (63)	5 (63)
Within 6 months	14 (61)	18 (78)	9 (60)	13 (87)	5 (63)	5 (63)
Within 12 months	14 (61)	20 (87)	9 (60)	13 (87)	5 (63)	7 (88)
No. of Subj. Evaluated for TTR and DOR (F)	14	18	9	12	5	6
Time to Response (months) Median (Min, Max)	1.2 (0.7, 4.1)	1.7 (0.7, 9.2)	0.8 (0.7, 4.1)	1.7 (0.7, 5.7)	1.6 (0.7, 1.6)	2.6 (1.6, 9.2)
Time to CR (months) Median (Min, Max) (C)	12.5 (5.4, 21.8)	5.3 (1.6, 19.9)	NC	10.8 (1.6, 19.9)	12.4 (5.4, 21.8)	5.3 (4.4, 9.2)
Time to PR (months) Median (Min, Max) (D)	0.8 (0.7, 4.1)	1.7 (0.7, 8.9)	0.82 (0.7, 4.1)	1.7 (0.7, 5.7)	1.17 (0.7, 1.6)	3.5 (1.6, 8.9)
DOR Median (95% CI) (B)	N.A. (7.43, N.A.)	N.A. (15.5, N.A.)	12.0 (1.8, N.A.)	N.A. (8.3, N.A.)	N.A. (1.9, N.A.)	N.A. (17.0, N.A.)
No. of Subj. with DOR of at Least						
12 months	6 (43)	9 (50)	3 (33)	7 (58)	3 (60)	2 (33)
18 months	4 (29)	4 (22)	2 (22)	3 (25)	2 (40)	1 (17)
Ongoing Response (E)	5 (36)	7 (39)	3 (33)	5 (42)	2 (40)	2 (33)

(B) Median computed using Kaplan-Meier Method (C) Subjects with BOR of CR. (D) Subjects with BOR of PR. (E) Subjects with Ongoing Response include responders who had neither progressed nor initiated subsequent therapy at the time of analysis, and excludes responders censored prior to 26 weeks of the clinical cutoff date. (F) Subjects CA209039-1-41 and CA209039-9-29 who had investigator-assessed disease progression per the protocol criteria before achieving response are excluded from calculation.
N.A.: Not available; NC: Not calculated

ASCT = autologous stem cell transplant; **BV** = brentuximab vedotin; **cHL** = classical Hodgkin lymphoma; **CR** = complete remission; **DOR** = duration of response; **IRRC**= Independent radiologic review committee; **NA**= not available; **ORR** = objective response rate; **PR** = partial remission; **TTR** = time to response

Source: [EPAR,2015 page 46/85][3]

Quality of Life

Quality of life (QoL) was measured in CHECKMATE-205 and results are publicly available for Cohort B (August 2015 data cut-off).[1, 4] Longer term results for Cohorts A, B, and C are not publicly available at the present time. The submitter provided the following statement on the pooled data: "when the data were pooled for Cohorts A, B, and C, nivolumab treatment resulted in clinically meaningful and statistically significant improvement in general and cancer-specific patient related outcomes. Improvement started early (Week 9) and persisted to Week 93".[5]

Patient-reported general health status and health-related QoL were assessed using the EQ-5D and the European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire-Core 36 (EORTC QLQC30). QoL assessments were performed on day 1 of cycle 1, and then every four cycles for the first 17 cycles, and then every six cycles thereafter.[1] Descriptive statistics were used to evaluate mean change in EORTC QLQ-C30 and EQ-5D scores from baseline to week 33. EQ-5D visual analogue scale (VAS) was summarised at each assessment time point, and analyses

evaluating mean score changes from baseline using the EORTC QLQ-C30 were performed in all treated patients who had an assessment at baseline and at least one subsequent assessment.[1]

As of 16-Jun-2014 data cut-off date, 72 out of 80 patients (90%) in cohort B, completed a baseline and at least one post-baseline EORTC QLQ-C30 or EQ-5D assessment. By week 33, 58% of patients were included. Least squares mean score change from baseline at week 33 was 19.1 (±3.1) for EQ-5D VAS and 7.6 (±2.3) for the EORTC QLQ-C30 global health/quality of life status scale (Table 6.9). For the global health status subscale, all subgroup estimates were consistent with the overall changes from baseline, except patients with absence of B symptoms who experienced significantly smaller changes at week 17 only. For other EORTC subscales statistically significant improvements in least squares mean from baseline were observed at each time point (fatigue, dyspnea, appetite loss, physical functioning, role functioning) Although all subgroup estimates were in line with the overall change, there were some trends for non-smokers (vs. smokers), ECOG PS 0 (vs. 1), USA/Canada (vs. Europe), and B symptoms at baseline (vs. none) toward better symptom improvement. Changes from baseline across responders and non-responders were consistent with overall changes from baseline.[1,4]

Table 6.9 EORTC-QLQ-C30 functional and Symptom Scale Summary in CHECKMATE-205 Cohort B

	Mean (SD) score	Mean change from baseline (SD)			
	Baseline (n=75)	Week 9 (n=64)	Week 17 (n=60)	Week 25 (n=51)	Week 33 (n=44)
Global health and functional subscales*					
Global health status	65.2 (25.2)	9.8 (19.0)	4.2 (20.9)	9.4 (21.5)	6.7 (24.2)
Physical functioning	77.6 (24.9)	7.5 (17.6)	5.5 (16.8)	7.1 (19.9)	4.9 (13.3)
Role functioning	69.8 (33.1)	10.7 (29.0)	5.1 (22.2)	7.1 (22.3)	6.1 (20.7)
Emotional functioning	78.1 (21.6)	4.4 (18.3)	–0.6 (20.4)	5.7 (20.6)	4.9 (11.9)
Cognitive functioning	87.1 (17.9)	0.6 (17.5)	–2.4 (19.7)	–1.0 (20.2)	0.0 (15.8)
Social Functioning	72.7 (28.6)	7.1 (24.8)	2.7 (26.9)	4.8 (27.2)	10.6 (23.5)
Symptom subscales†					
Fatigue	27.0 (28.9)	–8.1 (26.0)	–6.9 (23.3)	–9.8 (23.9)	–7.6 (20.1)
Nausea and vomiting	4.4 (14.3)	–2.0 (14.9)	0.0 (14.9)	–1.7 (16.0)	0.4 (19.9)
Pain	18.4 (21.5)	–8.2 (20.6)	–6.3 (22.6)	–7.8 (25.7)	–4.5 (22.4)
Dyspnea	23.1 (30.0)	–9.0 (23.0)	–4.8 (20.5)	–6.8 (24.5)	–4.1 (20.0)
Insomnia	29.8 (32.2)	–5.7 (28.5)	–4.2 (31.2)	–4.9 (27.5)	–12.2 (25.6)
Appetite loss	21.8 (30.3)	–9.0 (24.6)	–6.6 (25.0)	–7.5 (25.7)	–7.3 (26.4)
Constipation	11.6 (22.9)	–1.1 (30.9)	–3.0 (25.6)	–2.7 (28.7)	–8.1 (20.8)
Diarrhea	10.7 (25.2)	0.0 (24.8)	3.0 (26.4)	–2.0 (22.0)	–0.8 (19.0)
Financial difficulties	35.6 (36.1)	–8.5 (31.9)	–3.0 (32.6)	–5.4 (36.2)	–5.7 (27.8)

*Higher scores indicate higher health-related quality of life; positive changes indicate improvement in health-related quality of life from baseline. †Lower scores equal better symptom status; negative change scores indicate improvement in symptoms compared with baseline.

Source: Reprinted from The Lancet Oncology, Vol. 17 number 9, Younes A, Santoro A, Shipp M, et al., Nivolumab for classical Hodgkin's lymphoma after failure of both autologous stem-cell transplantation and brentuximab vedotin: a multicentre, multicohort, single-arm phase 2 trial, Page No. 10, Copyright (2016), with permission from Elsevier.[1]

Harms Outcomes

CHECKMATE-205

The assessment of safety was based on frequency of deaths, AEs, SAEs, AEs leading to discontinuation of study drug, AEs leading to dose delay, select AEs, and specific clinical laboratory assessments. All on-study AEs were summarized for the entire treatment period from the first dosing date to the last dosing date plus 30 days (primary safety analysis) and 100 days (Safety analysis for potentially due to late-occurring AEs). Safety was assessed using National

Cancer Institute Common Terminology Criteria for Adverse Events, version 4·0, and adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 18·0.[1]

As of October 2015 data cut-off, AEs of any cause were reported in 79/80 (99%) of patients in Cohort B; of those, 46 (58%) were grade 1 or 2, 26 (33%) were grade 3, and six (8%) were grade 4 AEs. One patient (1%) died from multi-organ failure that was deemed to be unrelated to the study treatment. A total of 71/80 (89%) patients had drug-related AEs, including 51 (64%) grade 1 or 2, 17 (21%) grade 3, and three (4%) grade 4 AEs. The most common drug-related adverse events were fatigue (25%) infusion-related reaction (20%), rash (16%), arthralgia (14%), pyrexia (14%), nausea (13%), diarrhoea (10%), and pruritus (10%). The most common drug-related grade 3–4 AEs were increased lipase and neutropenia. Serious adverse events of any cause were reported in 20/80 (25%) patients in Cohort B (Table 6.10). The most common serious AEs included pyrexia (4%), malignant neoplasm progression (3%), pneumonia (3%), arrhythmia (3%), meningitis (3%), and infusion-related reaction (3%). Drug-related serious AEs were reported in 5/80 (6%) patients, with the most common being infusion-related reaction (3%).[1]

Table 6.10: Serious Adverse Events in CHECKMATE-205 Cohort B, 05-Oct_2017 cut-off date

Event	Patients with adverse event (N=80)		
	Any grade	Grade 3–4	Grade 5
Total patients with an event	20 (25%)	10 (13%)	1 (1%)†
Pyrexia	3 (4%)	1 (1%)	0
Malignant neoplasm progression‡	2 (3%)	2 (3%)	0
Pneumonia	2 (3%)	1 (1%)	0
Arrhythmia	2 (3%)	1 (1%)	0
Meningitis	2 (3%)	1 (1%)	0
Infusion-related reaction	2 (3%)	0	0

Data are number (%).
*Listed are serious adverse events that were reported in at least 2% of patients. Includes events reported between the first dose and 30 days after the last dose of study therapy. †Multi-organ failure. ‡Includes progression of Hodgkin lymphoma.

Source: Reprinted from The Lancet Oncology, Vol. 17 number 9, Younes A, Santoro A, Shipp M, et al., Nivolumab for classical Hodgkin's lymphoma after failure of both autologous stem-cell transplantation and brentuximab vedotin: a multicentre, multicohort, single-arm phase 2 trial, Page No. 8, Copyright (2016), with permission from Elsevier.[1]

As of December 2016 data cut-off, the most common drug-related AEs in 243 nivolumab-treated patients (Cohorts A, B, and C) included fatigue (23%), diarrhea (15%), and infusion reactions (14%). The most common drug-related serious AEs were infusion reactions (2%) and pneumonitis (1%). Serious AEs included fatigue (1%), diarrhea (1%), rash (1%), infusion reactions (<1%), and autoimmune hepatitis (1%). The most common drug-related AEs which led to discontinuation of the study treatment were pneumonitis (2%) and autoimmune hepatitis (1%).[2] A detailed list of adverse events reported in CHECKMATE-205 participants (Cohorts A, B, and C) are shown in Table 6.11.

Table 6.11 Summary of Adverse events reported in all treated patients in CHECKMATE-205 trial, as of 16-Dec-2016 data cut-off date

	Number (%) Subjects	
	Cohort A+B+C (N = 243)	
DEATHS*	29 (11.9)	
WITHIN 30 DAYS OF LAST DOSE	6 (2.5)	
WITHIN 100 DAYS OF LAST DOSE	9 (3.7	
DUE TO STUDY DRUG TOXICITY	0	
	Any Grade	**Grade 3-4**
ALL CAUSALITY SAEs	66 (27.2)	45 (18.5)
DRUG-RELATED SAEs	29 (11.9)	16 (6.6)
ALL CAUSALITY AEs LEADING TO DC	22 (9.1)	11 (4.5)
DRUG-RELATED AEs LEADING TO DC	17 (7.0)	9 (3.7)
ALL-CAUSALITY AEs	241 (99.2)	99 (40.7)
Most Frequent AEs (≥ 20% of Any Grade)		
UPPER RESPIRATORY TRACT INFECTION	53 (21.8)	2 (0.8)
FATIGUE	85 (35.0)	3 (1.2)
PYREXIA	72 (29.6)	1 (0.4)
DIARRHOEA	86 (35.4)	2 (0.8)
COUGH	83 (34.2)	0
NAUSEA	52 (21.4)	0
DRUG-RELATED AEs	191 (78.6)	57 (23.5)
Most Frequent Drug-related AEs (≥ 10% of Any Grade)		
FATIGUE	56 (23.0)	2 (0.8)
DIARRHOEA	37 (15.2)	2 (0.8)
NAUSEA	25 (10.3)	0
RASH	29 (11.9)	2 (0.8)
PRURITUS	25 (10.3)	0
INFUSION RELATED REACTION	34 (14.0)	1 (0.4)
ALL CAUSALITY SELECT AES, BY CATEGORY		
ENDOCRINE	42 (17.3)	1 (0.4)
GASTROINTESTINAL	87 (35.8)	3 (1.2)
HEPATIC	37 (15.2)	14 (5.8)
PULMONARY	13 (5.3)	1 (0.4)
RENAL	12 (4.9)	3 (1.2)
SKIN	92 (37.9)	4 (1.6)
HYPERSENSITIVITY/INFUSION REACTIONS	43 (17.7)	3 (1.2)
DRUG-RELATED SELECT AES, BY CATEGORY		
ENDOCRINE	32 (13.2)	0
GASTROINTESTINAL	37 (15.2)	3 (1.2)
HEPATIC	29 (11.9)	11 (4.5)
PULMONARY	12 (4.9)	0
RENAL	5 (2.1)	1 (0.4)
SKIN	53 (21.8)	3 (1.2)
HYPERSENSITIVITY/INFUSION REACTIONS	39 (16.0)	2 (0.8)
ALL-CAUSALITY IMMUNE-MEDIATED ADVERSE EVENTS WITHIN 100 DAYS OF LAST DOSE, BY CATEGORY		
Immune-mediated AEs Treated with Immune-modulating medication		
DIARRHEA/COLITIS	6 (2.5)	5 (2.1)
HEPATITIS	12 (4.9)	10 (4.1)
PNEUMONITIS	10 (4.1)	0
NEPHRITIS AND RENAL DYSFUNCTION	1 (0.4)	1 (0.4)
RASH	21 (8.6)	4 (1.6)
HYPERSENSITIVITY/INFUSION REACTIONS	12 (4.9)	2 (0.8)
Immune-Mediated Endocrine AEs Treated with or without Immune-Modulating Medications		
ADRENAL INSUFFICIENCY	1 (0.4)	0
HYPOPHYSITIS	0	0
HYPOTHYROIDISM/THYROIDITIS	29 (11.9)	0
HYPERTHYROIDISM	6 (2.5)	0
DIABETES MELLITUS	2 (0.8)	1 (0.4)

MedDRA version 19.1; CTC version 4.0. All events are within 30 days of the last dose of study drug, unless otherwise indicated.
* Disease progression (18 subjects) was the most common cause of death.

Source: [CA209205 csr- May 2017, page 17][38]

CHECKMATE-039

The assessment of safety was based on the frequency of AEs, serious AEs, deaths, hematologic laboratory abnormalities, serum chemistry laboratory abnormalities, and changes in blood pressure and heart rate measurements. AEs were assessed continuously during the study and for 100 days after last treatment. Adverse events were coded using the most current version of MedDRA and evaluated according to the NCI CTCAE Version 4.0. Subjects were followed until all treatment-related adverse events have recovered to baseline or were deemed irreversible by the investigator.

At a median follow-up of 40 (range 0 to 75) weeks, the incidence of drug-related AEs of any grade that occurred in at least 5% of the patients was 78%. Grade 3 AEs were reported in 22% of patients

(Table 6.12). Overall, drug-related AEs were reported in 18 patients (78%). The most common AEs included rash (22%) and a decreased platelet count (17%). Drug-related grade 3 AEs were reported in 5 patients (22%), and included the myelodysplastic syndrome, pancreatitis, pneumonitis, stomatitis, colitis, gastrointestinal inflammation, thrombocytopenia, an increased lipase level, a decreased lymphocyte level, and leukopenia. No drug-related grade 4 or 5 adverse events were reported. Three patients had one serious drug-related adverse event each (grade 3 pancreatitis, grade 3 myelodysplastic syndrome, and grade 2 lymph-node pain) (Table 6.12). No treatment-related deaths were reported. Twelve patients (52%) discontinued treatment; of those, two patients (9%) had toxic events (the myelodysplastic syndrome and thrombocytopenia).[6]

Table 6.12 Adverse events at a median follow up period of 40 weeks in CHECKMATE-039

Event	Any Grade	Grade 3
	no. of patients (%)	
Any adverse event	18 (78)	5 (22)
Drug-related adverse events reported in ≥5% of patients		
Rash	5 (22)	0
Decreased platelet count	4 (17)	0
Fatigue	3 (13)	0
Pyrexia	3 (13)	0
Diarrhea	3 (13)	0
Nausea	3 (13)	0
Pruritus	3 (13)	0
Cough	2 (9)	0
Hypothyroidism	2 (9)	0
Decreased lymphocyte count	2 (9)	1 (4)
Hypophosphatemia	2 (9)	0
Hypercalcemia	2 (9)	0
Increased lipase level	2 (9)	1 (4)
Stomatitis	2 (9)	1 (4)
Drug-related serious adverse events		
Myelodysplastic syndrome	1 (4)	1 (4)
Lymph-node pain	1 (4)	0
Pancreatitis	1 (4)	1 (4)

* No grade 4 or grade 5 drug-related adverse events were reported. Decisions about whether the adverse event was related to the study drug were made by the investigators. A more detailed list of adverse events is provided in Table S1 in the Supplementary Appendix.

Source: From The New England Journal of Medicine, Stephen M. Ansell, Alexander M. Lesokhin, Ivan Borrello, et al, PD-1 Blockade with Nivolumab in Relapsed or Refractory Hodgkin's Lymphoma, Volume No. 372, Page No 315. Copyright © (2018) Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.[6]

After a median follow-up of 86 (range 32 to 107) weeks, a total of three patients discontinued nivolumab due to AEs (one each, grade 2 peripheral neuropathy, grade 3 myelodysplastic syndrome, and grade 3 pancreatitis). Grade 1 or 2 immune-related AEs occurred in 4 of 10 patients who had durable responses per protocol (Table 6.13). These AEs were resolved without treatment in two patients. The incidence of immune-related AEs did not increase with time on treatment.[7]

Table 6.13 Adverse events at a median follow up period of 86 weeks in CHECKMATE-039

Adverse Event	cHL (n = 23)	
	Any Grade, n (%)	Resolved, %
Gastrointestinal	**4 (17)**	
Diarrhea	3 (13)	100
Colitis	1 (4)	100
Hepatic	**2 (9)**	
ALT increased	1 (4)	100
AST increased	1 (4)	100
Blood alkaline phosphatase increased	1 (4)	0
Pulmonary	**1 (4)**	
Pneumonitis	1 (4)	100
Skin	**5 (22)**	
Rash	4 (17)	100
Pruritus	3 (13)	100
Pruritic rash	1 (4)	100
Skin hypopigmentation	1 (4)	0
Endocrine disorders		
Hyperthyroidism	4 (17)	75
Hypersensitivity/infusion reaction	**2 (9)**	
Bronchospasm	1 (4)	100
Infusion-related reaction	1 (4)	100

Source: Republished with permission of Blood: journal of the American Society of Hematology, from Nivolumab in Patients (Pts) with Relapsed or Refractory Classical Hodgkin Lymphoma (R/R cHL): Clinical Outcomes from Extended Follow-up of a Phase 1 Study (CA209-039), Stephen Ansell, Philippe Armand, John M. Timmerman, et al., 126, 2015; permission conveyed through Copyright Clearance Center, Inc.[7]

6.4 Ongoing Trials

No ongoing trials were identified.

7 SUPPLEMENTAL QUESTIONS

The following supplemental questions were identified during development of the review protocol as relevant to the pCODR review of nivolumab for with Classical Hodgkin Lymphoma (cHL) who have relapsed or progressed after autologous stem cell transplantation (ASCT) and brentuximab vedotin (BV); or three or more lines of systemic therapy:

- Summary and critical appraisal of the Manufacturer-submitted indirect treatment comparison of nivolumab to BV and best supportive care (BSC) in relapsed or refractory classical Hodgkin lymphoma after failure of ASCT

Topics considered in this section are provided as supporting information. The information has not been systematically reviewed.

7.1 Summary and critical appraisal of the Manufacturer-submitted indirect treatment comparison of nivolumab to BV and BSC in relapsed or refractory classical Hodgkin lymphoma after failure of ASCT

7.1.1 Objective

The pCODR-conducted literature search did not identify any RCTs that included a direct, head-to-head comparison between nivolumab and other potential treatment options in classical Hodgkin Lymphoma (cHL) who have relapsed or progressed after:

- autologous ASCT and BV, or
- three or more lines of systemic therapy including ASCT (BV-naïve patients).

In the absence of direct comparative evidence, indirect comparison (ITC) of nivolumab with relevant comparators in the two aforementioned patient subgroups was required.

The objective of this section is to summarize and critically appraise the Manufacturer-submitted ITC that provides evidence for the efficacy of nivolumab versus available treatment options in patients with relapsed or refractory cHL.

7.1.2 Findings

Review of Manufacturer's ITC[8]

7.1.2.1 Objectives of ITC

The objective of the Manufacturer's ITC was to conduct an indirect comparison of nivolumab against BV, and BSC in patients with cHL who have failed ASCT.

Of note, the ITC analysis did not include all comparators relevant to the submitted funding request. The ITC analysis compared the effects of nivolumab with BV and BSC (mix of chemotherapies) in patients who failed ASCT and were BV-naïve (Cohort A of CHECKMATE-205). The ITC analysis did not include a comparison between nivolumab and a potential comparator (e.g. chemotherapy regimens or pembrolizumab) in patients who have failed both ASCT and subsequent BV treatment (cohort B) or in those who have had ASCT and BV in any treatment order (BV before and/or after ASCT) (cohort C).

7.1.2.2 Overview of Methods

Systematic Review

The Manufacturer conducted a systematic review to identify eligible studies that were published up to March 2017, for inclusion in the ITC.[41]

The following data bases were searched: MEDLINE and MEDLINE in-process (OVID SP), EMBASE (OVID SP), The Cochrane Central Register of Controlled Trials (CENTRAL), and PubMed. Additional searches were conducted in the following ongoing trials registers were accessed to identify relevant trials: the metaRegister of Controlled Trials on www.controlledtrials.com; the US National Institutes of Health Ongoing Trials Register on www.clinicaltrials.gov; and the World Health Organization International Clinical Trials Registry Platform on www.who.int/trialsearch. The searches were supplemented with the grey literature search and searches of conference proceedings, from the past two years, of the: European Society of Medical Oncology congress; American Society of Clinical Oncology annual meeting; International Symposium on Hodgkin Lymphoma; American Society of Hematology annual meeting; European Hematology Association congress; and International Congress on Malignant Lymphoma.

Table 7.1: Study selection criteria used in the Manufacturer-submitted systematic review

Population	Individuals with relapsed or refractory cHL who have failed: • >1 chemotherapy and ASCT (and BV-naïve) • ASCT and BV • >2 prior therapies (and are not candidates for ASCT)
Intervention(s)	Any intervention
Comparator(s)	Not specified
Outcome(s)	Efficacy • Objective response rate (investigator-assessed, IRRC assessed) • Complete response (investigator-assessed, and IRRC assessed) • Partial response (investigator-assessed, and IRRC assessed) • Duration of response • Treatment duration • Progression-free survival (investigator-assessed, and IRRC assessed • Overall survival Safety • Overall treatment discontinuation • Discontinuation due to grade 3/4 AEs
Study design	• Randomized controlled trials • Non-randomized clinical trials • Single-arm clinical trials • Prospective or retrospective observational studies

AEs = adverse events; **ASCT** = autologous stem cell transplantation; **BV** = brentuximab vedotin; **IRRC** = independent radiologic review committee

Source: [Manufacturer-submitted systematic literature review on efficacy and safety of therapies for relapsed or refractory cHL][41]

The literature search resulted in a total of 2,990 abstracts, 93 of which underwent full text review. The study selection criteria are summarized in Table 7.1. Thirty-two citations were identified as eligible for data extraction and synthesis. An independent double screening and data extraction process was used for study selection.[41] An additional 17 citations were identified

through hand searching of reference lists and conference proceedings. The systematic literature search identified a total of 49 eligible articles, of which:

- Eleven articles reported on nine studies of patients who had previously received ASCT and BV. None of the nine studies reported both response rates and median OS.
- Thirty eight articles reported on 35 studies of patients who had previously received ASCT and were BV-naïve. Of these 35 studies, 11 reported both overall response rates and median OS, while 12 reported overall response rates and PFS.

Assessment of Study Quality

No formal study quality assessment was conducted.[5] The Manufacturer clarified during the checkpoint meeting that each of the studies included to inform the model were "*reviewed in detail, and authors were contacted as needed to ensure integrity and correct interpretation of results*".[5]

Indirect Treatment Comparisons[8]

Due to the paucity of the available evidence in the populations of the interest, and the lack of comparative trials, the Manufacturer did not deem it feasible to perform a formal network meta-analysis. Therefore, they based their indirect comparison on:

a) an unadjusted (naïve) ITC, comparing the areas under curve (AUC) for individuals receiving nivolumab versus individuals receiving BV, and BSC; and

b) a matched-adjusted indirect treatment comparison (MAIC) of the AUC for individuals receiving nivolumab versus individuals receiving BV, and BSC. This statistical technique would allow for weighting individual patient-level data (IPD) of one population to match baseline characteristics reported for a comparable population for which only aggregate data are available.

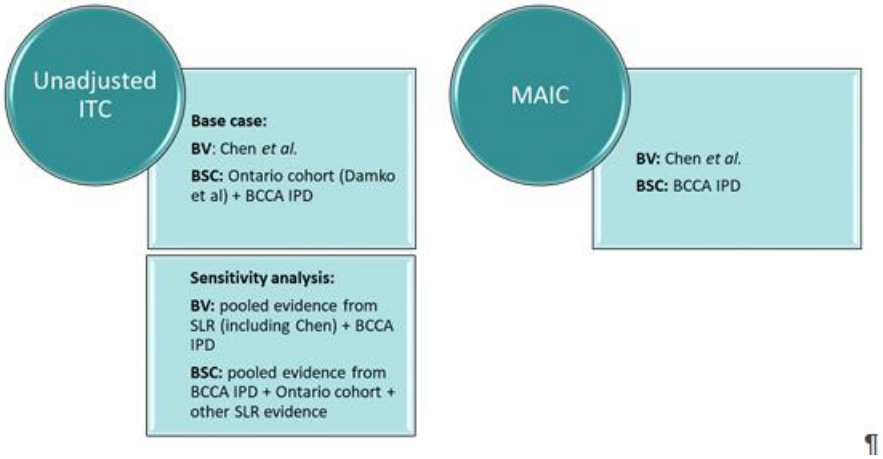
The following data sources were used for the purposes of these analyses (Figure 7.1):

- For nivolumab:
  IPD from cohort A of the CHECKMATE-205 trial (patients who failed ASCT and were BV-naïve [n = 63]),[40] which included interim data after a median follow up of 19.1 months for this study cohort. At the time of data cut-off, 41% and 10% of patients had experienced disease progression and death, respectively.

- For BV:
  Primary source – the final results of the BV pivotal clinical trial, reported by Chen et al.[n=102].[13]
  Secondary sources –Three observational studies, identified through the systematic literature review (described above), which reported survival outcomes associated with BV;[42-44] and observational IPD (patients who received BV after ASCT failure [n=5]) obtained from the British Columbia Cancer Agency (BCCA) Lymphoid Cancer Database.[8]

- For BSC:
  Primary source – IPD from the BCCA Lymphoid Cancer Database (patients who failed ASCT [n=88], pooled with survival data from a cohort of cHL patients from Ontario, Canada [n=122].[8]
  Secondary source – Four observational studies, identified through the systematic literature review, which reported survival outcomes associated with BSC.[11,45-47]

Figure 7.1 Data sources used to inform indirect treatment comparisons



BCCA = British Columbia Cancer Agency; **BV** = brentuximab vedotin; **IPD** = individual patient data; **ITC** = indirect treatment comparison; **MAIC** = matched-adjusted indirect treatment comparison; **SLR** = systematic literature review; **BSC** = best supportive care

Source: [Manufacturer-submitted ITC report][8]

Unadjusted ITC[8]

The unadjusted ITC was performed based on comparisons of areas under the overall survival (OS) and progression-free survival (PFS) curves for nivolumab, BV, and BSC. This was done primarily by conducting non-parametric Kaplan-Meier analyses, followed by parametric model-based survival analyses (without covariates), for both PFS and OS. Whenever the follow up data was insufficient to accurately predict the tail of the PFS and/or OS curves (e.g., in the nivolumab study), different assumptions about the tail of those curves were made through clinical expert opinion, and experiences with the drugs of interest in other indications, where available, and scenario analyses were performed.

To estimate the incremental survival benefit of nivolumab relative to each of the comparators, incremental AUC was calculated by taking the difference in AUC for the different combinations of curves, for a total of four comparisons (2 nivolumab curves x 1 BV curve + 2 nivolumab curves x 1 BSC curve). A long-term time horizon of 15 years was selected for comparing AUC between nivolumab and comparators. To estimate confidence intervals for the AUC estimates, a bootstrapping approach was used.

Matched-Adjusted Indirect Comparison[8]

The MAIC was conducted using the IPD from the nivolumab trial, and the BCCA Lymphoid Cancer Database, to match baseline summary characteristics from Chen et al., which was the main source of evidence for BV. The MAIC followed the same approach described for the previously described unadjusted comparisons; however, a MAIC analysis allowed for a comparison of treatment outcomes adjusting for imbalances across studies on key prognostic factors.

The following patient characteristics that were available in the BV trial publications as well as in the nivolumab IPD were considered for matching: age, sex, race, Eastern Cooperative Oncology Group (ECOG) performance status, presence of B-symptoms, bone marrow involvement, prior radiation or radiotherapy, number of prior chemotherapy regimens, median time from initial diagnosis to first dose of study drug, best response achieved with most recent systemic regimen, number of prior ASCTs, and stage at initial diagnosis. However, a subset of baseline characteristics

available, which were either considered to be a prognostic factor for survival or a known treatment effect-modifier, was selected for adjustment. Individuals in the IPD population were weighted by the inverse of their propensity score, to balance the distribution of the baseline characteristics in the IPD population with that of the target aggregate population.

7.1.2.3 Results of ITC

Unadjusted ITC[8]

Model-based (best-fitting models) unadjusted comparisons of survival curves for nivolumab versus BV, and Nivolumab versus BSC suggested that, over a 15-year time horizon:

- Expected PFS in patients who received nivolumab was shorter by 5.2 months than that of patients receiving BV (Incremental PFS –5.2; 95% CI –30.1, 25.1), and the selected PFS curves for nivolumab and BV crossed in the long-term.
- Expected PFS in patients who received nivolumab was estimated to be 14.4 months (Incremental PFS 14.4; 0.95% CI –4.8, 41.8) longer than that of patients receiving BCS.
- Expected OS in patients who were treated with nivolumab was estimated to be 22.2 months longer than that of patients receiving BV (Incremental OS 22.2; 95% CI -38.6, 92.3).
- Expected OS in patients who were treated with nivolumab was estimated to be 39.8 months longer than patients receiving BSC (Incremental OS 39.8; 95% CI -18.4, 108.3).

For the above-mentioned conservative models, the incremental PFS and OS benefits of nivolumab over BV did not reach statistical significance (all 95% CIs included the null hypothesis value of zero).

Matched-Adjusted Indirect Comparison[8]

Nivolumab versus BV

MAIC analysis of nivolumab versus BV was performed using IPD from cohort A of the CHECKMATE-205 trial (patients who failed ASCT and were BV-naïve [n = 63]), and the BV pivotal clinical trial publication [Chen et al; n=102].[13]

Baseline characteristics considered for matching included: Sex, ECOG performance score, presence of B-symptoms at diagnosis, and prior cancer-related radiotherapy. The original and weighted values for these variables are shown in Table 7.2.

The Manufacturer provided the following reasons for not matching other potentially relevant baseline characteristics:

- The number of prior chemotherapy regimens was not included for matching as this variable was skewed for nivolumab, and the mean would differ from the median.
- The number of prior ASCTs was not included for matching as only one nivolumab patient had two prior ASCTs, and including this variable was significantly reducing the effective sample size.
- Age was not included for matching as median age was similar between nivolumab (median age: 33) and BV (median age: 31).
- Bone marrow involvement was not included for matching as this variable was similar between nivolumab (3%) and BV (8%).
- Stage of disease at initial diagnosis and median time form initial diagnosis, and race were not considered as a prognostic factor or effect-modifier.
- Primary refractory disease, disease status (relapsed or refractory) relative to most recent prior therapy, best response achieved with most recent systemic regimen, and median PFS

for most recent regimen were not included for matching because data on these variables was not available for nivolumab.

As can be seen in Table 7.2, The effective sample size after matching was reduced to 42, which accounts for a 33.5% reduction from the original sample size (N=63).

Table 7.2. MAIC weights for the baseline characteristics matched for indirect comparison of nivolumab versus brentuximab vedotin

·Baseline·characteristics·with·original·and·weighted·estimates¶

¤	Nivolumab¤		Brentuximab·vedotin·(n=102)¤
Baseline·characteristic¤	Before·matching·(n=63)¤	After·matching·(n=42)¤	
Female,·n·(%)¤	29·(46)¤	26·(53)¤	·54·(53)¤
ECOG·≥1,·n·(%)¤	24·(38)¤	29·(59)¤	60·(59)¤
B-symptoms,·n·(%)¤	10·(16)¤	17·(34)¤	35·(34)¤
Prior·radiotherapy¤	37·(59)¤	33·(66)¤	67·(66)¤

·ECOG: Eastern Cooperative Oncology Group↵

¶

Source: [Manufacturer-submitted ITC report- Table 10][8]

The original and reweighted PFS curves for nivolumab, along with the original PFS curve for BV, are shown in Figure 7.2. As the figure shows, the reweighted PFS (per investigator) curve for nivolumab lies below the original curve; while the reweighted PFS (per IRRC) curve is similar to the original curve.

The original and reweighted OS curves for nivolumab, along with the original OS curve for BV, are shown in Figure 7.3. As the figure shows, the reweighted OS curve for nivolumab lies below the original curve.

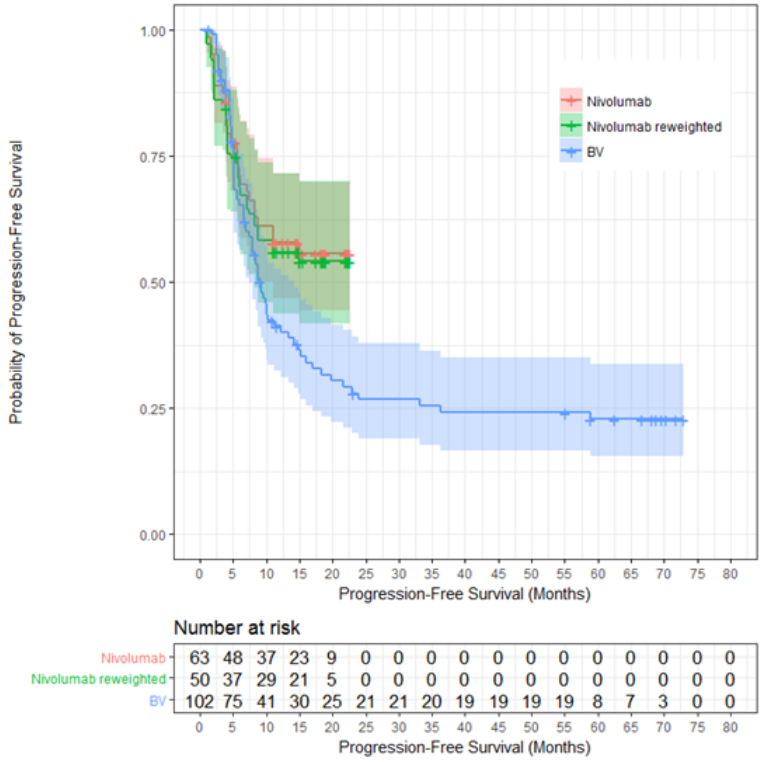
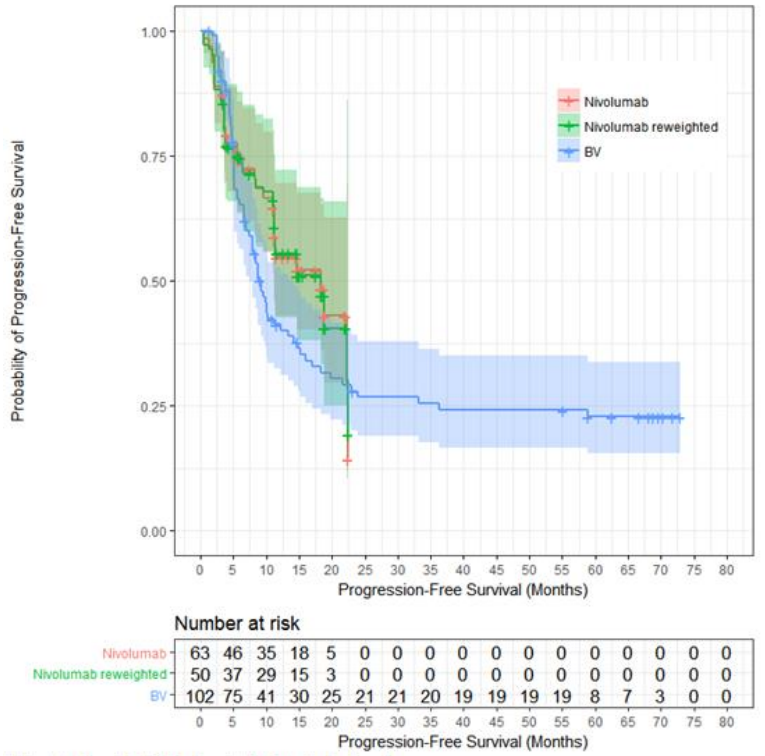
Due to the short follow up in the nivolumab trial, no statistical tests were conducted to estimate the incremental survival benefit of nivolumab relative to BV. Instead, the Manufacturer provided the results of model-based comparisons (over a 15-year time horizon), as explained in section 7.1.2.2.

The best-fitting (conservative) parametric models for the MAIC analysis of nivolumab versus BV suggested that, over a 15-year time horizon:

- Expected PFS in patients who received nivolumab was shorter by 5.4 months than that of patients receiving BV (Incremental PFS -5.4; 95% CI -33.3, 27.4).
- Expected OS in patients who were treated nivolumab was estimated to be 33.6 months longer than that of patients receiving BV (Incremental OS 33.6; 95% CI -8.2, 84.1)

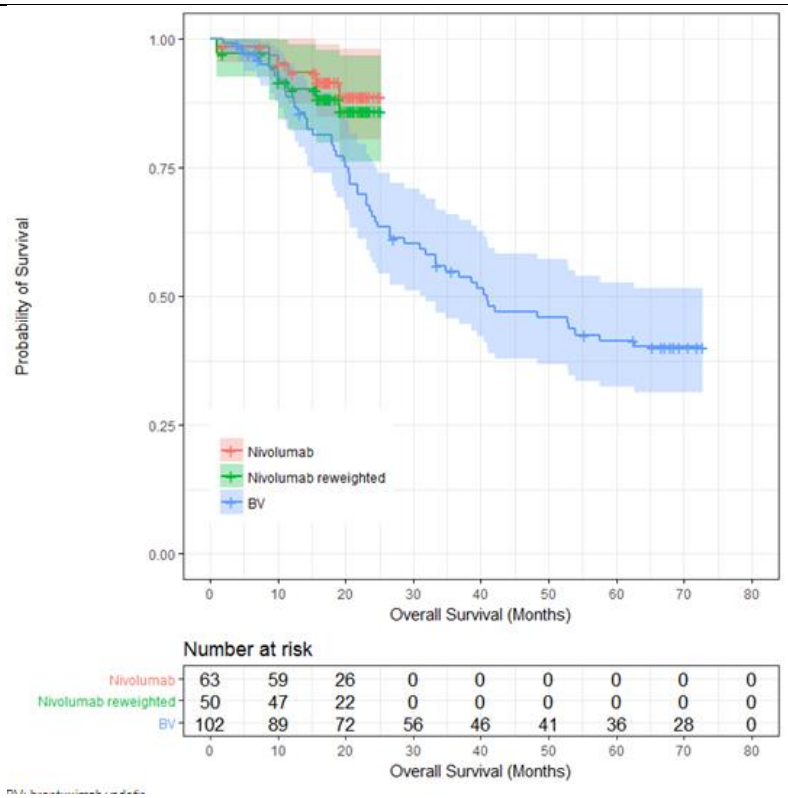
For the above-mentioned best-fitting (conservative) models, the incremental PFS and OS benefits of nivolumab over BV did not reach statistical significance (95% CIs included the null hypothesis value of zero).

Figure 7.2: Kaplan-Meier curves of progression-free survival for nivolumab and brentuximab

Investigator-assessed	IRRC-assessed
	

Source: [Manufacturer-submitted ITC report][8]

Figure 7.2: Kaplan-Meier curves of overall survival for nivolumab and brentuximab



Shaded areas represent 95% confidence bands. The sample size for nivolumab (n=50) reported in the 'Number at risk' table is the sum of the weights, and different from the estimate of effective sample size.

Source: [Manufacturer-submitted ITC report][8]

Nivolumab versus BSC[8]

MAIC analysis of nivolumab versus BSC was performed using integrated IPD from cohort A of the CHECKMATE-205 trial (patients who failed ASCT and were BV-naïve [n = 63]), survival data from a cohort of cHL patients from Ontario, Canada [n=122].[8]

Baseline characteristics considered for matching included: Sex, presence of B-symptoms at diagnosis, ABVD chemotherapy as first line treatment, age<50 years, and hemoglobin level less than 100 g/L. The original and weighted values for these variables are shown in Table 7.3. All nivolumab patients had either ABVD (Adriamycin [doxorubicin], bleomycin, vinblastine, dacarbazine) or BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone) chemotherapy regimens as a first line therapy. Therefore, the Manufacturer included an indicator of first line ABVD for matching, and did not include indicators for "other" or "none".

The Manufacturer provided the following reasons for not matching other potentially relevant baseline characteristics:

- Stage at diagnosis was not included for matching as it was not considered a prognostic factor.
- Bulky disease at diagnosis was not included for matching as it was only available for nivolumab patients at baseline.

- Lactase Dehydrogenase and ECOG were not included for matching as these variables were highly missing for BSC.
- Median time to ASCT (months) was not included for matching as it was similar between nivolumab (19 months) and BSC (21 months).

As can be seen in Table 7.3, The effective sample size after matching was reduced to 48, which accounts for a 23.5% reduction from the original sample size (N=63).

Table 7.3. MAIC weights for the baseline characteristics matched for indirect comparison of nivolumab versus Best Supportive Care

Baseline characteristic	Nivolumab		BSC (n=122) %
	Before matching (n=63)	After matching (n=48)	
Female, n (%)	29 (46)	22 (39)	39
B-symptoms at diagnosis, n (%)	35 (55)	33 (60)	60
ABVD as first line of therapy, n (%)	47 (75)	48 (87)	87
Time to relapse after ASCT < 6 months, n (%)	19 (30)	23 (41)	41
Age < 50, n (%)	52 (83)	45 (82)	82
Hemoglobin < 100, n (%)	6 (10)	11 (19)	19

ASCT = autologous stem cell transplant; BSC = best supportive care.
Source: [Manufacturer-submitted ITC report][8]

The original and reweighted PFS curves for nivolumab, along with the original PFS curve for BSC, are shown in Figure 7.4. As the figure shows, the reweighted PFS curve for nivolumab lies below the original curve.

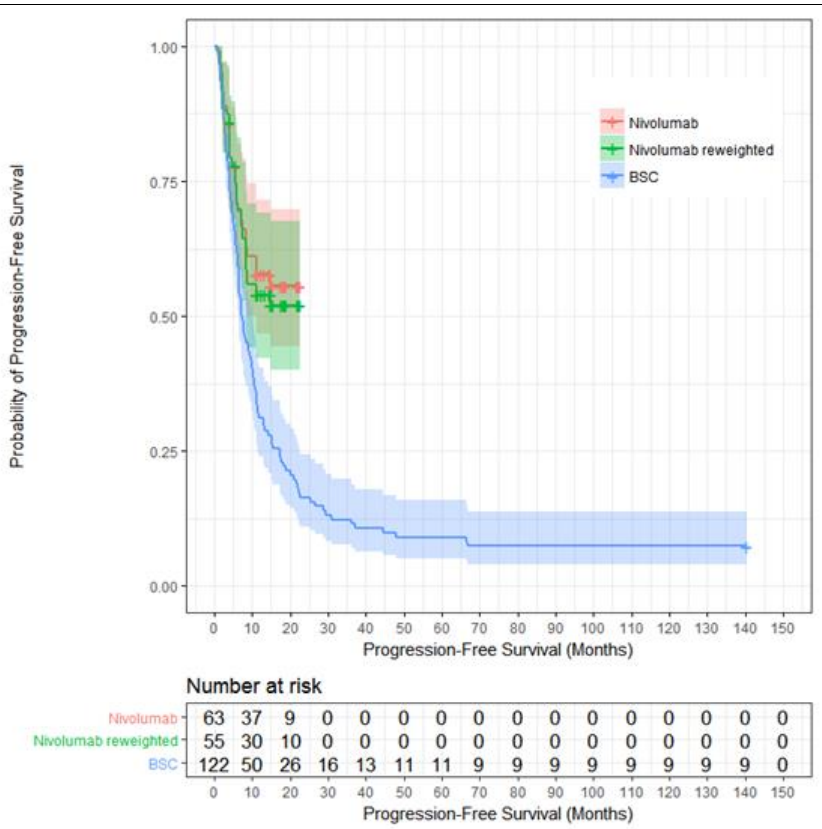
The original and reweighted OS curves for nivolumab, along with the original OS curve for BSC, are shown in Figure 7.5. As the figure shows, the reweighted OS curve for nivolumab lies below the original curve.

Due to the short follow up in the nivolumab trial, no statistical tests were conducted to estimate the incremental survival benefit of nivolumab relative to BSC. Instead, the Manufacturer provided the results of model-based comparisons (over a 15-year time horizon), as explained in section 7.1.2.2.

The best-fitting parametric models for the MAIC analysis of nivolumab versus BSC suggested that, over a 15-year time horizon:

- Expected PFS in patients who received nivolumab was 13.0 months longer than that of patients receiving BSC (Incremental PFS 13.0; 95% CI –6.7, 43.3). However, this PFS benefit did not reach statistical significance (the 95% CI included the null hypothesis value of zero)
- Expected OS in patients who were treated nivolumab was estimated to be 59.2 months longer than that of patients receiving BSC (Incremental OS 59.2; 95% CI 20.1, 107.3).

Figure 7.4: Kaplan-Meier curves of progression-free survival for nivolumab and Best Supportive Care

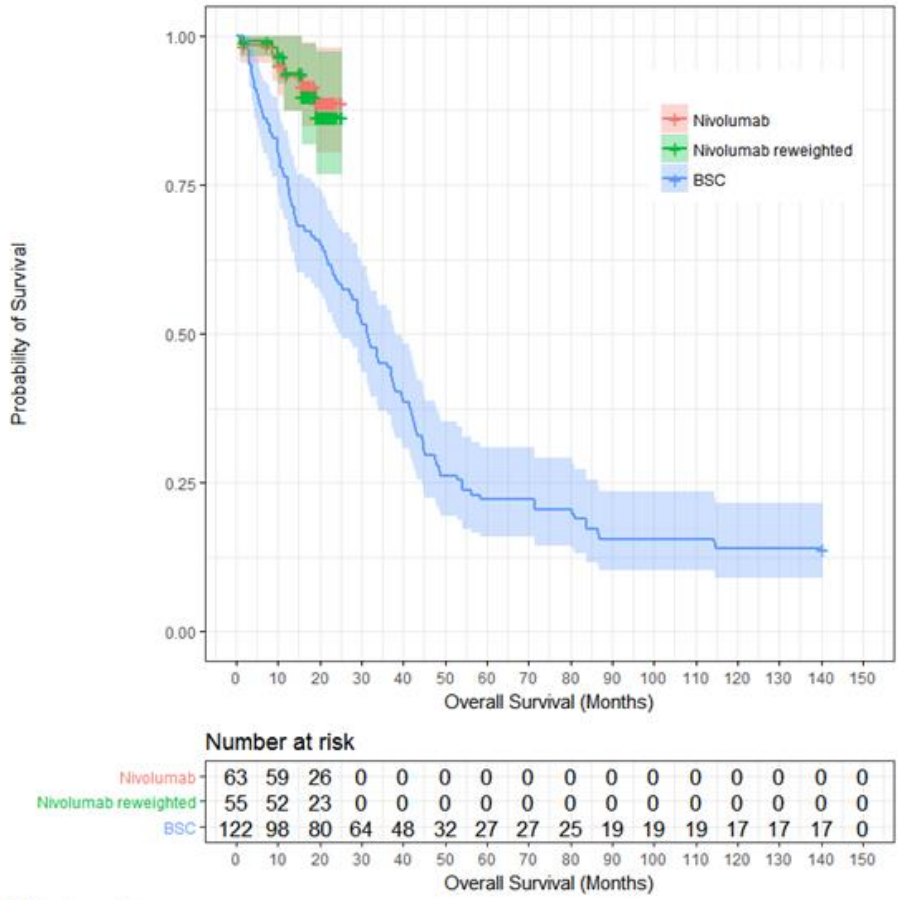


BSC = best supportive care.

Shaded areas represent 95% confidence bands. The sample size for nivolumab (n=55) reported in the 'Number at risk' table is the sum of the weights, and different from the effective sample size.

Source: [Manufacturer-submitted ITC report][8]

Figure 7.5: Kaplan-Meier curves of overall survival for nivolumab and Best Supportive Care



BSC = best supportive care.

Shaded areas represent 95% confidence bands. The sample size for nivolumab (n=55) reported in the 'Number at risk' table is the sum of the weights, and different from the effective sample size.

Source: [Manufacturer-submitted ITC report][8]

7.1.3 Summary

The quality of the ITC provided by the Manufacturer[8] was assessed according to the recommendations made by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Task Force on Indirect Treatment Comparisons.[48] Details of the critical appraisal are presented in Table 7.4.

Table 7.4: Adapted ISPOR Questionnaire to Assess the Credibility of an Indirect Treatment Comparison or Network Meta-Analysis†

ISPOR Questions	Details and Comments
1. Is the population relevant?	**Yes, in part.** The indication for this review was to assess the efficacy and safety of nivolumab for treatment of adult patients with Classical Hodgkin Lymphoma (cHL) who have relapsed or progressed after: 1) autologous stem cell transplantation (ASCT) and brentuximab vedotin (BV) (aligned with CHECKMATE-205 Cohort B and Cohort C);[5] or

ISPOR Questions		Details and Comments
		2) three or more lines of systemic therapy including ASCT (aligned with CHECKMATE-205 Cohort A);[5] For the purpose of the ITC analysis, the Manufacturer used data from CHECKMATE-205 Cohort A (i.e., patients who failed ASCT and were BV-naïve) to perform indirect comparison of nivolumab against BV, and BSC. The ITC analysis did not compare effects of nivolumab with potential comparators, such as BSC or pembrolizumab, in patients who failed both ASCT and BV (CHECKMATE-205 Cohorts B and C). The issue related to the lack of indirect comparisons of nivolumab with potential comparators in patients similar CHECKMATE-205 Cohorts B or C discussed with the Manufacturer during the checkpoint meeting [5] After the meeting, pCODR requested the Manufacturer to provide both clinical and cost-effectiveness data addressing a comparison of nivolumab to pembrolizumab in the population base case decision problem 2 (i.e., patients who receive ASCT and subsequent BV).[5] The Manufacturer acknowledged that the Keynote-087 study Cohort 1 seemed to correspond with the CHECKMATE-205 Cohort B. However, they stated that treatment comparisons were "*hindered by lack of, or access to, appropriate clinical endpoints for pembrolizumab*".[5] In their response the Manufacturer clarified that PFS and OS curves needed for an ITC analysis were not accessible publicly for pembrolizumab.[5]
2.	Are any critical interventions missing?	**Yes, in part.** The Manufacturer included BV and BSC for patients who failed on ASCT and were BV-naïve. However, as described in Question 1 (above) potentially relevant comparators for patients who failed on both ASCT and BV (including pembrolizumab) were not included in the ITC.
3.	Are any relevant outcomes missing?	**Yes, in part.** In the ITC, the Manufacturer estimated PFS and OS. Safety or HRQoL outcomes were not considered for this analysis.
4.	Is the context (e.g., settings and circumstances) applicable to your population?	**Yes, in part.** The trials and observational studies included in the ITC had a number of between-study differences in terms of baseline characteristics of study populations. In addition to a naïve ITC, the Manufacturer used matched-adjusted indirect comparisons (MAICs) to reduce observed between-trial differences.
5.	Did the researchers attempt to identify and include all relevant randomized controlled trials?	**Yes.** The Manufacturer provided a summary of the systematic literature review process used in the ITC.[41] In the summary, the Manufacturer took adequate steps to ensure an unbiased selection of studies for inclusion in their analysis. They described the information sources they used, their search strategy, their study selection criteria, and independent double screening and data extraction.
6.	Do the trials for the interventions of interest form one connected network of randomized controlled trials?	**No.** The Manufacturer stated that a standard NMA approach was not feasible due to the limited data available in the population of interest; particularly the lack of comparative trials. Therefore, they performed a simplified ITC that was based on the comparison of the area under the survival curves, as well as a MAIC analysis. Because the follow up data for the

ISPOR Questions		Details and Comments
		nivolumab study was insufficient, both the naïve and MAIC comparisons of survival curves were based on parametric models, which were informed by different assumptions (about the tail of survival curves) made through clinical expert opinion, Manufacturer's experiences with the drugs of interest in other indications, where available, and scenario analyses.
7.	Is it apparent that poor quality studies were included thereby leading to bias?	**Maybe**. No formal study quality assessment was conducted.[5] The Manufacturer clarified during the checkpoint meeting that each of the studies included to inform the model were "reviewed in detail, and authors were contacted as needed to ensure integrity and correct interpretation of results".[5] Considering the fact that, in the submitted ITC, survival curves were digitized based on pooled data from clinical trials and observational studies, an assessment of the methodological quality of the included studies would have been of particular value in increasing the robustness of the ITC results.
8.	Is it likely that bias was induced by selective reporting of outcomes in the studies?	**Maybe**. The ITC included PFS and OS as the study outcomes. Safety outcomes were not considered in the analysis. In the MAICs, the sample sizes dropped by 33.5%, and 23.5% for the comparisons of nivolumab vs BV and nivolumab vs BSC, respectively, after matched-adjustment for the baseline variables. This reduction in the sample sizes might result in reduction in the statistical power.
9.	Are there systematic differences in treatment effect modifiers (i.e. baseline patient or study characteristics that impact the treatment effects) across the different treatment comparisons in the network?	**Yes.** The Manufacturer provided a descriptive comparison of baseline variables which were considered for MAIC analysis. No qualitative or quantitative assessment of between-study heterogeneity was provided. The following variables were considered for matching: age, sex, race, Eastern Cooperative Oncology Group (ECOG) performance status, presence of B-symptoms, bone marrow involvement, prior radiation or radiotherapy, number of prior chemotherapy regimens, median time from initial diagnosis to first dose of study drug, best response achieved with most recent systemic regimen, number of prior ASCTs, and stage at initial diagnosis. However, a subset of baseline characteristics available, which were either considered to be a prognostic factor or a known effect-modifier, was selected for adjustment. However, a number of variables with higher missing values for one of the study treatments were not included in the matching.
10.	If yes (i.e. there are such systematic differences in treatment effect modifiers), were these imbalances in effect modifiers across the different treatment comparisons identified prior to comparing individual study results?	**Yes, in part**. The Manufacturer adjusted for the prognostic baseline variables or potential effect-modifiers for which data was available; however, due to the limited data it is difficult to judge about other potential effect-modifiers that might act as a source of bias in the analysis.
11.	Were statistical methods used that preserve within-study randomization? (No naïve comparisons)	**Not applicable**. No RCTs were included in the ITC.
12.	If both direct and indirect comparisons are available for pairwise contrasts (i.e. closed loops), was agreement in treatment effects	**Not applicable**. There was no closed loop.

ISPOR Questions		Details and Comments
	(i.e. consistency) evaluated or discussed?	
13.	In the presence of consistency between direct and indirect comparisons, were both direct and indirect evidence included in the network meta-analysis?	**Not applicable**. There was no closed loop.
14.	With inconsistency or an imbalance in the distribution of treatment effect modifiers across the different types of comparisons in the network of trials, did the researchers attempt to minimize this bias with the analysis?	**Yes.** In addition to a naïve ITC, the Manufacturer performed a MACI analysis of to adjust the imbalance of treatment effects across the included studies.
15.	Was a valid rationale provided for the use of random effects or fixed effect models?	**Not applicable**.
16.	If a random effects model was used, were assumptions about heterogeneity explored or discussed?	**Not applicable**.
17.	If there are indications of heterogeneity, were subgroup analyses or meta-regression analysis with pre-specified covariates performed?	A MACI was conducted with the aim of reducing heterogeneity. Subgroup analysis or meta-regression analysis were not performed.
18.	Is a graphical or tabular representation of the evidence network provided with information on the number of RCTs per direct comparison?	**No.** The Manufacturer used single arm trials and observational studies for the purpose of ITC, and provided a graphical illustration of sources of data for each type of analysis. No graphical or tabular representation of the evidence network provided.
19.	Are the individual study results reported?	**Yes, in part.** The Manufacturer did not provide individual study results from the included observational. The baseline characteristics of the trials used in MAIC were provided in the ITC report, as well as the number of population at risk and observed event rates for the estimates of PFS and OS.
20.	Are results of direct comparisons reported separately from results of the indirect comparisons or network meta-analysis?	**Not applicable.**
21.	Are all pairwise contrasts between interventions as obtained with the network meta-analysis reported along with measures of uncertainty?	**Yes.** The Manufacturer provided the 95% CI for PFS and OS estimates (both crude and incremental estimates).
22.	Is a ranking of interventions provided given the reported treatment effects and its uncertainty by outcome?	**No**.
23.	Is the impact of important patient characteristics on treatment effects reported?	**No**. No covariates were included in the analysis.
24.	Are the conclusions fair and balanced?	The ITC report provided by the Manufacturer concluded that while clinical data for nivolumab was still immature, the available data demonstrated a survival benefit, and hence a clinical value, for nivolumab, when compared with BV and BSC. However, the Methods Team felt that no clear conclusions can be drawn due to the immature survival data for nivolumab, as well as inherent limitations of naïve or model-based indirect

ISPOR Questions		Details and Comments
		comparisons (e.g., multiple assumptions in the absence of sufficient data).
25.	Were there any potential conflicts of interest?	**Not reported.**
26.	If yes, were steps taken to address these?	**Not applicable.**

HRQoL = health-related quality of life; **ISPOR** = International Society For Pharmacoeconomics and Outcomes Research; ITC = indirect treatment comparison; **PFS** = progression-free survival; **OS** = overall survival.
† Adapted from Jansen, Value Health. 2014;17(2):157-73[48]

Conclusion

The submitted ITC was conducted to assess the relative efficacy of nivolumab compared with BV and BSC for the management of patients with relapsed or refractory cHL. The Manufacturer performed naïve indirect treatment comparisons (with no adjustment for prognostic factors or effect-modifiers), supplemented with a MAICs, which allowed for matching baseline characteristics of the study populations, and comparing individual patient level data from one trial with aggregate data from other studies. The MAIC used data from CHECKMATE-205 Cohort A (BV-naïve) to perform indirect comparison of nivolumab against BV, and BSC.

Due to the short follow up in the included nivolumab study (CHECKMATE-205), different scenarios were considered to quantify uncertainty around the expected PFS and OS benefits, over a 15-year time horizon, for nivolumab. Under the most conservative scenarios, in patients who received nivolumab the expected PFS was 5.4 months shorter, and the expected OS was 33.6 months longer than those of patients receiving BV. However, the incremental PFS and OS benefits of nivolumab over BV did not reach statistical significance. Nivolumab OS was estimated to be between 59.2 months longer than that of patients receiving BSC.

Although the results of the submitted ITC suggest that nivolumab is associated with a survival benefit in patients with relapsed or refractory cHL, these results should be interpreted with caution due to the limitations that arise from the lack of comparative evidence, insufficient follow-up data for nivolumab studies, lack of quality appraisal for the included studies, lack of indirect comparisons for safety and QoL data, and the use of naïve and model-based indirect comparisons. Therefore, the relative efficacy of nivolumab over BV or BSC remains uncertain in cHL patients who failed on ASCT and were BV-naïve. Furthermore, because the submitted ITC did not include cHL patients who failed on both ASCT and BV, no conclusions can be made on the relative efficacy of nivolumab compared to its potential comparators (e.g., pembrolizumab and BSC) in this patient population.

8 COMPARISON WITH OTHER LITERATURE

None identified.

9 ABOUT THIS DOCUMENT

This Clinical Guidance Report was prepared by the pCODR Lymphoma Clinical Guidance Panel and supported by the pCODR Methods Team. This document is intended to advise the pCODR Expert Review Committee (pERC) regarding the clinical evidence available on nivolumab for classical Hodgkin Lymphoma. Issues regarding resource implications are beyond the scope of this report and are addressed by the relevant pCODR Economic Guidance Report. Details of the pCODR review process can be found on the CADTH website (www.cadth.ca/pcodr).

pCODR considers it essential that pERC recommendations be based on information that can be publicly disclosed. Information included in the Clinical Guidance Report was handled in accordance with the pCODR Disclosure of Information Guidelines.

This Final Clinical Guidance Report is publicly posted at the same time that a pERC Final Recommendation is issued. The Final Clinical Guidance Report supersedes the Initial Clinical Guidance Report. Note that no revision was made in between posting of the Initial and Final Clinical Guidance Reports.

The Lymphoma Clinical Guidance Panel is comprised of 3 medical oncologists. The panel members were selected by the pCODR secretariat, as outlined in the pCODR Nomination/Application Information Package, which is available on the CADTH website (www.cadth.ca/pcodr). Final selection of the Clinical Guidance Panels was made by the pERC Chair in consultation with the pCODR Executive Director. The Panel and the pCODR Methods Team are editorially independent of the provincial and territorial Ministries of Health and the provincial cancer agencies.

APPENDIX A: LITERATURE SEARCH STRATEGY AND DETAILED METHODOLOGY

Literature search via OVID platform

CCTR, Embase, Ovid MEDLINE(R)

Line #	Search Strategy	Results
1	(Nivolumab* or Opdivo* or MDX1106 or MDX-1106 or BMS 936558 or BMS936558 or HSDB 8256 or HSDB8256 or ONO 4538 or ONO4538 or 31YO63LBSN or 946414-94-4).ti,ab,ot,kf,kw,hw,rn,nm.	7765
2	*nivolumab/ or (Nivolumab* or Opdivo* or MDX1106 or MDX-1106 or BMS 936558 or BMS936558 or HSDB 8256 or HSDB8256 or ONO 4538 or ONO4538 or 31YO63LBSN).ti,ab,kw.	5038
3	Hodgkin Disease/ or Hodgkin*.ti,ab,kw. or ((lymphoma* or lymphogranuloma* or granuloma*) and malignan*).ti,ab,kw. or Reed-Sternberg*.ti,ab,kw.	259029
4	Hodgkin Disease/	85336
5	Hodgkin*.ti,ab,kf,kw.	153893
6	((lymphoma* or lymphogranuloma* or granuloma*) and (cancer* or neoplasm* or malignan*)).ti,ab,kf,kw.	182380
7	(Reed adj2 Sternberg*).ti,ab,kf,kw.	5454
8	or/4-7	305278
9	1 and 8	662
10	9 use ppez	133
11	9 use cctr	51
12	Hodgkin Disease/	85336
13	Hodgkin*.ti,ab,kw.	153478
14	((lymphoma* or lymphogranuloma* or granuloma*) and (cancer* or neoplasm* or malignan*)).ti,ab,kw.	180983
15	(Reed adj2 Sternberg*).ti,ab,kw.	5447
16	or/12-15	303844

17	2 and 16	433
18	17 use oemezd	258
19	18 and conference abstract.pt.	90
20	limit 19 to yr="2012 -Current"	90
21	18 not 19	168
22	10 or 11 or 21	352
23	remove duplicates from 22	245
24	20 or 23	335

1. Literature search via PubMed

A limited PubMed search was performed to capture records not found in MEDLINE.

Search	Query	Items found
#4	Search **#5 AND #6 AND #7**	7
#3	Search **publisher[sb]**	528902
#2	Search **Hodgkin Disease[mh] OR Hodgkin*[tiab] OR ((lymphoma*[tiab] OR lymphogranuloma*[tiab] OR granuloma*[tiab]) AND malignan*[tiab]) OR Reed-Sternberg*[tiab]**	101941
#1	Search **"nivolumab" [Supplementary Concept] OR Nivolumab*[tiab] or Opdivo*[tiab] or MDX1106[tiab] or MDX-1106[tiab] or BMS 936558[tiab] or BMS936558[tiab] or HSDB 8256[tiab] or HSDB8256[tiab] or ONO 4538[tiab] or ONO4538[tiab] or 31YO63LBSN[tiab] or 946414-94-4[rn]**	1531

2. Cochrane Central Register of Controlled Trials (Central)

Searched via Ovid

3. Grey Literature search via:

Clinical trial registries:

U.S. NIH ClinicalTrials.gov
http://www.clinicaltrials.gov/

Canadian Partnership Against Cancer Corporation. Canadian Cancer Trials
http://www.canadiancancertrials.ca/

Search: Nivolumab/Opdivo; Hodgkin Lymphoma

Select international agencies including:

Food and Drug Administration (FDA):
http://www.fda.gov/

European Medicines Agency (EMA):
http://www.ema.europa.eu/

Search: Nivolumab/Opdivo, Hodgkin Lymphoma

Conference abstracts:

American Society of Clinical Oncology (ASCO)
http://www.asco.org/

American Society of Hematology (ASH)
http://www.hematology.org/

Search: Nivolumab/Opdivo, Hodgkin Lymphoma - last 5 years

Literature Search Methods

The literature search was performed by the pCODR Methods Team using the search strategy provided in Appendix A.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946-) with in-process records & daily updates via Ovid; Embase (1974-) via Ovid; The Cochrane Central Register of Controlled Trials via Ovid; and PubMed. 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, Opdivo 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, but not limited by publication year.

The search is considered up to date as of January 30 2018.

Grey literature (literature that is not commercially published) was identified by searching the websites of regulatory agencies (Food and Drug Administration and European Medicines Agency), clinical trial registries (U.S. National Institutes of Health – clinicaltrials.gov and Canadian Partnership Against Cancer Corporation - Canadian Cancer Trials), and relevant conference abstracts. Conference abstracts were retrieved through a search of the Embase database limited to the last five years. Abstracts from the American Society of Clinical Oncology (ASCO) and the American Society of Hematology (ASH) were searched manually for conference years not available

in Embase. Searches were supplemented by reviewing the bibliographies of key papers and through contacts with the Clinical Guidance Panel. In addition, the Manufacturer of the drug was contacted for additional information as required by the pCODR Review Team.

Study Selection

One member of the pCODR Methods Team selected studies for inclusion in the review according to the predetermined protocol. All articles considered potentially relevant were acquired from library sources. One member of the pCODR Methods Team made the final selection of studies to be included in the review.

Included and excluded studies (with reasons for exclusion) are identified in section 6.3.1.

Quality Assessment

Assessment of study bias was performed by one member of the pCODR Methods Team with input provided by the Clinical Guidance Panel and other members of the pCODR Review Team. SIGN-50 Checklists were applied as a minimum standard. Additional limitations and sources of bias were identified by the pCODR Review Team.

Data Analysis

No additional data analyses were conducted as part of the pCODR review.

Writing of the Review Report

This report was written by the Methods Team, the Clinical Guidance Panel and the pCODR Secretariat:

- The Methods Team wrote a systematic review of the evidence and summaries of evidence for supplemental questions.
- The pCODR Clinical Guidance Panel wrote a summary of background clinical information and the interpretation of the systematic review. The Panel provided guidance and developed conclusions on the net clinical benefit of the drug.
- The pCODR Secretariat wrote summaries of the input provided by patient advocacy groups, by the Provincial Advisory Group (PAG), and by Registered Clinicians.

REFERENCES

1. Younes A, Santoro A, Shipp M, Zinzani PL, Timmerman JM, Ansell S, et al. Nivolumab for classical Hodgkin's lymphoma after failure of both autologous stem-cell transplantation and brentuximab vedotin: a multicentre, multicohort, single-arm phase 2 trial. Lancet Oncol [Internet]. 2016 Sep [cited 2017 Oct 19];17(9):1283-94. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5541855/pdf/nihms882539.pdf

2. Fanale M, Engert A, Younes A, Armand P, Ansell S, Zinzani PL, et al. Nivolumab for relapsed/refractory classical Hodgkin lymphoma after autologous transplant: full results after extended follow-up of the phase 2 checkmate 205 trial [abstract]. Hematological oncology. 2017;Conference: 14th international conference on malignant lymphoma palazzo dei congressi. Switzerland. 35(Suppl 2):135-6.

3. Committee for Medicinal Products for Human Use (CHMP). Assessment report: Opdivo (nivolumab) [Internet]. London (GB): European Medicines Agency; 2015 Jul 16. [cited 2017 Nov 7]. (European public assessment report). Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/003985/WC500219972.pdf

4. Engert A, Taylor F, Bennett B, Hirji I, Cocks K, McDonald J, et al. Patient subgroup analysis of quality-of-life outcomes in checkmate 205, a phase 2 study of nivolumab in patients with classical hodgkin lymphoma. Blood [Internet]. 2016 [cited 2017 Oct 19];Conference: 58th annual meeting of the american society of hematology, ASH. 2016. United states. Conference start: 20161203. Conference end: 20161206 128(22) (no pagination). Available from: http://www.bloodjournal.org/content/128/22/1831

5. BMS response to pCODR checkpoint meeting questions on Opdivo® (nivolumab) for relapsed/refractory classical Hodgkin's lymphoma [additional manufacturer's information]. Montreal (PQ): Bristol-Myers Squibb Canada Co; 2017 Nov 20.

6. Ansell SM, Lesokhin AM, Borrello I, Halwani A, Scott EC, Gutierrez M, et al. PD-1 blockade with nivolumab in relapsed or refractory Hodgkin's lymphoma. N Engl J Med. 2015 Jan 22;372(4):311-9. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4348009

7. Ansell S, Armand P, Timmerman JM, Shipp MA, Garelik MBB, Zhu L, et al. Nivolumab in patients (PTS) with relapsed or refractory classical hodgkin lymphoma (R/R Chl): Clinical outcomes from extended follow-up of a phase 1 study (CA209-039). Blood [Internet]. 2015 [cited 2017 Oct 19];126(23):583. Available from: http://www.bloodjournal.org/content/126/23/583

8. The relative efficacy of nivolumab to brentuximab vedotin and best supportive care in relapsed or refractory classical Hodgkin lymphoma after failure of ASCT: An indirect treatment comparison [CONFIDENTIAL internal manufacturer's report]. Vancouver (BC): Broad Street Health Economics & Outcomes Research; 2017 Sep 1.

9. Canadian Cancer Society's Advisory Committee on Cancer Statistics. Canadian cancer statistics 2017 [Internet]. Toronto (ON): Canadian Cancer Society; 2017. [cited 2018 Jan 30]. Available from: http://www.cancer.ca/~/media/cancer.ca/CW/publications/Canadian%20Cancer%20Statistics/Canadian-Cancer-Statistics-2017-EN.pdf

10. Van Den NE, Casasnovas O, Andre M, Touati M, Senecal D, Edeline V, et al. Classical Hodgkin's lymphoma: the Lymphoma Study Association guidelines for relapsed and refractory adult patients eligible for transplant. Haematologica. 2013 Aug;98(8):1185-95. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3729898

11. Moskowitz AJ, Perales MA, Kewalramani T, Yahalom J, Castro-Malaspina H, Zhang Z, et al. Outcomes for patients who fail high dose chemoradiotherapy and autologous stem cell rescue for relapsed and primary refractory Hodgkin lymphoma. Br J Haematol. 2009 Jul;146(2):158-63. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3278667

12. Younes A, Gopal AK, Smith SE, Ansell SM, Rosenblatt JD, Savage KJ, et al. Results of a pivotal phase II study of brentuximab vedotin for patients with relapsed or refractory Hodgkin's lymphoma. J Clin Oncol. 2012 Jun 20;30(18):2183-9. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3646316

13. Chen R, Gopal AK, Smith SE, Ansell SM, Rosenblatt JD, Savage KJ, et al. Five-year survival and durability results of brentuximab vedotin in patients with relapsed or refractory Hodgkin lymphoma. Blood. 2016 Sep 22;128(12):1562-6. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC5034737

14. Cheah CY, Chihara D, Horowitz S, Sevin A, Oki Y, Zhou S, et al. Patients with classical Hodgkin lymphoma experiencing disease progression after treatment with brentuximab vedotin have poor outcomes. Ann Oncol. 2016 Jul;27(7):1317-23.

15. Wang M, Ma X, Guo L, Xia F. Safety and efficacy profile of pembrolizumab in solid cancer: pooled reanalysis based on randomized controlled trials. Drug Des Devel Ther. 2017;11:2851-60. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC5628692

16. Chen R, Zinzani PL, Fanale MA, Armand P, Johnson NA, Brice P, et al. Phase II Study of the Efficacy and Safety of Pembrolizumab for Relapsed/Refractory Classic Hodgkin Lymphoma. J Clin Oncol. 2017 Jul 1;35(19):2125-32.

17. Prasad V, Kaestner V. Nivolumab and pembrolizumab: Monoclonal antibodies against programmed cell death-1 (PD-1) that are interchangeable. Semin Oncol. 2017 Apr;44(2):132-5.

18. Chen BJ, Chapuy B, Ouyang J, Sun HH, Roemer MG, Xu ML, et al. PD-L1 expression is characteristic of a subset of aggressive B-cell lymphomas and virus-associated malignancies. Clin Cancer Res. 2013 Jul 1;19(13):3462-73. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4102335

19. Herst J, Crump M, Baldassarre FG, MacEachern J, Sussman J, Hodgson D, et al. Management of Early-stage Hodgkin Lymphoma: A Practice Guideline. Clin Oncol (R Coll Radiol). 2017 Jan;29(1):e5-e12.

20. Carde P, Karrasch M, Fortpied C, Brice P, Khaled H, Casasnovas O, et al. Eight Cycles of ABVD Versus Four Cycles of BEACOPPescalated Plus Four Cycles of BEACOPPbaseline in Stage III to IV, International Prognostic Score >/= 3, High-Risk Hodgkin Lymphoma: First Results of the Phase III EORTC 20012 Intergroup Trial. J Clin Oncol. 2016 Jun 10;34(17):2028-36.

21. Meyer RM, Gospodarowicz MK, Connors JM, Pearcey RG, Wells WA, Winter JN, et al. ABVD alone versus radiation-based therapy in limited-stage Hodgkin's lymphoma. N Engl J Med. 2012 Feb 2;366(5):399-408. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3932020

22. Kuruvilla J, Keating A, Crump M. How I treat relapsed and refractory Hodgkin lymphoma. Blood. 2011 Apr 21;117(16):4208-17.

23. Devizzi L, Santoro A, Bonfante V, Viviani S, Balzarini L, Valagussa P, et al. Vinorelbine: an active drug for the management of patients with heavily pretreated Hodgkin's disease. Ann Oncol. 1994 Nov;5(9):817-20.

24. Little R, Wittes RE, Longo DL, Wilson WH. Vinblastine for recurrent Hodgkin's disease following autologous bone marrow transplant. J Clin Oncol. 1998 Feb;16(2):584-8.

25. Venkatesh H, Di BN, Flynn TP, Vellek MJ, Boehm KA, Asmar L. Results of a phase II multicenter trial of single-agent gemcitabine in patients with relapsed or chemotherapy-refractory Hodgkin's lymphoma. Clin Lymphoma. 2004 Sep;5(2):110-5.

26. Bartlett NL, Niedzwiecki D, Johnson JL, Friedberg JW, Johnson KB, van BK, et al. Gemcitabine, vinorelbine, and pegylated liposomal doxorubicin (GVD), a salvage regimen in relapsed Hodgkin's lymphoma: CALGB 59804. Ann Oncol. 2007 Jun;18(6):1071-9.

27. Marcais A, Porcher R, Robin M, Mohty M, Michalet M, Blaise D, et al. Impact of disease status and stem cell source on the results of reduced intensity conditioning transplant for Hodgkin's lymphoma: a retrospective study from the French Society of Bone Marrow Transplantation and Cellular Therapy (SFGM-TC). Haematologica. 2013 Sep;98(9):1467-75. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3762105

28. Robinson SP, Sureda A, Canals C, Russell N, Caballero D, Bacigalupo A, et al. Reduced intensity conditioning allogeneic stem cell transplantation for Hodgkin's lymphoma: identification of prognostic factors predicting outcome. Haematologica. 2009 Feb;94(2):230-8. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2635413

29. Thomson KJ, Peggs KS, Smith P, Cavet J, Hunter A, Parker A, et al. Superiority of reduced-intensity allogeneic transplantation over conventional treatment for relapse of Hodgkin's lymphoma following autologous stem cell transplantation. Bone Marrow Transplant. 2008 May;41(9):765-70.

30. Sureda A, Canals C, Arranz R, Caballero D, Ribera JM, Brune M, et al. Allogeneic stem cell transplantation after reduced intensity conditioning in patients with relapsed or refractory Hodgkin's lymphoma. Results of the HDR-ALLO study - a prospective clinical trial by the Grupo Espanol de Linfomas/Trasplante de Medula Osea (GEL/TAMO) and the Lymphoma Working Party of the European Group for Blood and Marrow Transplantation. Haematologica. 2012 Feb;97(2):310-7. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3269494

31. European Public Assessment Report (EPAR): Adcetris (brentuximab vedotin) [Internet]. London (GB): European Medicines Agency; 2012. [cited 2018 Jan 31]. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002455/human_med_001588.jsp&mid=WC0b01ac058001d124

32. Gopal AK, Chen R, Smith SE, Ansell SM, Rosenblatt JD, Savage KJ, et al. Durable remissions in a pivotal phase 2 study of brentuximab vedotin in relapsed or refractory Hodgkin lymphoma. (1528-0020 (Electronic)).

33. Moskowitz CH, Nademanee A, Masszi T, Agura E, Holowiecki J, Abidi MH, et al. Brentuximab vedotin as consolidation therapy after autologous stem-cell transplantation in patients with Hodgkin's lymphoma at risk of relapse or progression (AETHERA): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2015 May 9;385(9980):1853-62.

34. Younes A, Ansell SM. Novel agents in the treatment of Hodgkin lymphoma: Biological basis and clinical results. Semin Hematol. 2016 Jul;53(3):186-9. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC5572135

35. Roemer MG, Advani RH, Ligon AH, Natkunam Y, Redd RA, Homer H, et al. PD-L1 and PD-L2 Genetic Alterations Define Classical Hodgkin Lymphoma and Predict Outcome. J Clin Oncol. 2016 Aug 10;34(23):2690-7. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC5019753

36. National Heart, Lung, and Blood Institute (NHLBI). Study of Nivolumab in Patients With Classical Hodgkin's Lymphoma (Registrational) (CheckMate 205). 2014 Jul 14 [cited 2017 Nov 9]. In: ClinicalTrials.gov [Internet]. Bethesda (MD): U.S. National Library of Medicine; 2000 - . Available from: https://clinicaltrials.gov/ct2/show/study/NCT00417417 NLM Identifier: NCT02181738.

37. National Heart, Lung, and Blood Institute (NHLBI). An Investigational Immuno-Therapy Study to Determine the Safety and Effectiveness of Nivolumab and Daratumumab, With or Without Pomalidomide and Dexamethasone, in Patients With Multiple Myeloma. 2012 May 7 [cited 2017 Nov 9]. In: ClinicalTrials.gov [Internet]. Bethesda (MD): U.S. National Library of Medicine; 2000 - . Available from: https://clinicaltrials.gov/ct2/show/study/NCT01592370?term=nivolumab&type=Intr&cond=Hodgkin+Lymphoma&cntry1=NA%3AUS&age=12&phase=0&rank=8 NLM Identifier: NNCT01592370.

38. Clinical Study Report: CA209205. Non-Comparative, Multi-Cohort, Single-Arm, Open-Label, Phase 2 Study of Nivolumab (BMS-936558) in Classical Hodgkin Lymphoma (cHL) Subjects [CONFIDENTIAL internal manufacturer's report]. Lawrenceville (NJ): Bristol-Myers Squibb; 2017 May 9.

39. Interim Clinical Study Report: CA209039. A phase 1 dose escalation study to investigate teh safety, pharmacokinetics, immunoregulatory activity, abd preliminary antitumour activity of anti-programmed-death 1 (PD-1) antibody (nivolumab, BMS-936558) abnd teh combinations of nivolumab and ipilmumab or nivolumab and lirilumab in subjects with relapsed or refactory hematologic malignancy [CONFIDENTIAL internal manufacturer's report]. Willinford (CT): Bristol-Myers Squibb; 2016 Jan 15.

40. pan-Canadian Oncology Drug Review manufacturer submission: OPDIVO™ (nivolumab), Intravenous Infusion, 10 mg nivolumab /mL; 40 mg and 100 mg single-use vials. Company: Bristol-Myers Squibb Canada Co. Montreal (PQ): Bristol-Myers Squibb Canada Co.; 2017 Sep 29.

41. Efficacy and safety of therapies for relapsed or refractory Hodgkin lymphoma: A review of the literature [CONFIDENTIAL internal manufacturer document]. Vancouver (BC): Broadstreet Health Economics and Outcomes Research; 2017 Mar 31.

42. Salihoglu A, Elverdi T, Karadogan I, Paydas S, Ozdemir E, Erdem G, et al. Brentuximab vedotin for relapsed or refractory Hodgkin lymphoma: experience in Turkey. Ann Hematol. 2015 Mar;94(3):415-20. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4317523

43. Tsirigotis P, Vassilakopoulos TP, Bousiou Z, Mpatsis I, Ghirkas K, Sakellari I. Salvage treatment of patients with relapsed/refractory hodgkin lymphoma with brentuximab vedotin: The greek experience. Haematologica. 2017;100(suppl 1):454-5. (Presented at 20th Congress of the European Hematology Association; 11-14 Jun 2015; Vienna, (AT)).

44. Zinzani PL, Viviani S, Anastasia A, Vitolo U, Luminari S, Zaja F, et al. Brentuximab vedotin in relapsed/refractory Hodgkin's lymphoma: the Italian experience and results of its use in daily clinical practice outside clinical trials. Haematologica. 2013 Aug;98(8):1232-6. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3729903

45. Karuturi MS, Arai S, Chen RW, Gopal AK, Feng L, Yuan Y, et al. Overall Survival Benefit for Patients with Relapsed Hodgkin Lymphoma Treated with Brentuximab Vedotin After Autologous Stem Cell Transplant. Blood. 2012;120:3701.

46. Kaloyannidis P, Voutiadou G, Baltadakis I, Tsirigotis P, Spyridonidis A, Repousis P, et al. Outcomes of Hodgkin's lymphoma patients with relapse or progression following autologous hematopoietic cell transplantation. Biol Blood Marrow Transplant. 2012 Mar;18(3):451-7.

47. Martinez C, Canals C, Sarina B, Alessandrino EP, Karakasis D, Pulsoni A, et al. Identification of prognostic factors predicting outcome in Hodgkin's lymphoma patients relapsing after autologous stem cell transplantation. Ann Oncol. 2013 Sep;24(9):2430-4.

48. Jansen JP, Trikalinos T, Cappelleri JC, Daw J, Andes S, Eldessouki R, et al. Indirect treatment comparison/network meta-analysis study questionnaire to assess relevance and credibility to inform health care decision making: an ISPOR-AMCP-NPC Good Practice Task Force report. Value Health. 2014 Mar;17(2):157-73.