CADTH | pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Clinical Guidance Report

Nivolumab (Opdivo) for Squamous Cell Carcinoma of the Head and Neck

August 31, 2017

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The pan-Canadian Oncology Drug Review is funded collectively by the provinces and territories with the exception of Quebec, which does not participate in pCODR at this time.

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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 squamous cell carcinoma of the head and neck. 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 squamous cell carcinoma of the head and neck conducted by the Head and Neck 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 squamous cell carcinoma of the head and neck, a summary of submitted Provincial Advisory Group Input on nivolumab (Opdivo) for squamous cell carcinoma of the head and neck, and a summary of submitted Registered Clinician Input on nivolumab (Opdivo) for squamous cell carcinoma of the head and neck, and are provided in Sections 2, 3, 4, and 5 respectively.

1.1 Introduction

The objective of this review is to evaluate the safety and efficacy of nivolumab (Opdivo) for the treatment of patients with recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN) whose disease had progressed within 6 months after platinum-based chemotherapy.

While a standard treatment option is not available in this setting, treatment options may include docetaxel which showed a superior response rate compared to methotrexate in a randomized phase II trial. Capecitabine, cetuximab, and paclitaxel with or without carboplatin may also be considered based on limited evidence.[9] Notably, cetuximab is not available in most jurisdictions and does not have regulatory approval for use in this setting. The Health Canada market authorization for nivolumab is for the treatment of recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN) in adults progressing on or after platinum-based therapy.

The recommended dose if nivolumab is 3mg/kg administered intravenously over 60 minutes every 2 weeks. Continue treatment as long as 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 one randomized, open-label, phase III trial comparing nivolumab to standard therapy in patients with recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN) whose disease had progressed within 6 months after platinum-based chemotherapy.[2] Adult patients were eligible to enroll in the trial if they had an Eastern Cooperative Oncology Group (ECOG) status of 0 or 1; histologically confirmed, recurrent or metastatic SCCHN of the oral cavity, pharynx, or larynx that was not amenable to curative treatment; tumour progression or recurrence within 6 months after the last dose of platinum-

containing chemotherapy administered as adjuvant therapy or in the context of primary or recurrent disease; adequate bone marrow, hepatic, and renal function; and measurable disease according to Response Evaluation Criteria In Solid Tumors (RECIST) 1.1.

Patients were randomized on a 2:1 ratio to receive nivolumab at 3 mg/kg of body weight every 2 weeks or to standard therapy, which consisted of a single-agent therapy of the investigator's choice (N = 121). Here, patients could have been treated with methotrexate (40-60 mg/m^2; N= 46), docetaxel (30-40 mg/m^2; N = 52) or cetuximab (400 mg/m^2 followed by 200 mg/m^2; N = 15).[2] Of note, cetuximab is not approved or available for use in this indication in Canada. Treatment beyond initial progression was allowed for both the nivolumab and standard therapy treatment groups at the investigator's discretion. A protocol amendment allowed patients in the standard therapy to receive nivolumab beyond initial progression.[3] The rationale for this amendment was based on a recommendation made by the independent Data Monitoring Committee (DMC) of Checkmate 141. On 26-Jan-2016, the DMC evaluated the interim analysis of overall survival and declared that nivolumab was superior to standard therapy. Based on this decision, the protocol was amended so that eligible patients assigned to standard therapy could receive subsequent nivolumab therapy in the Nivolumab Extension Phase.[3]

Efficacy

The primary outcome in Checkmate 141 was overall survival. The trial was stopped early because it met the pre-specified threshold for superiority by demonstrating superior overall survival with nivolumab as compared to standard therapy.[2] Median overall survival was 7.49 months (95% CI: 5.49 to 9.10) in the nivolumab group and 5.06 months (95% CI: 4.04 to 6.05) in the standard therapy group.[2] Treatment with nivolumab was associated with a reduced risk of death as compared to standard therapy (HR: 0.70, 97.73% 0.51 to 0.96; P = 0.01).[2]

Key secondary outcomes included progression free survival (PFS) and objective response rate (ORR).[2] There was no difference between treatment groups on PFS (HR: 0.89, 95% CI: 0.70 to 1.13; P = 0.32) or on ORR (nivolumab: 13.3% [95% CI: 9.3 to 18.3] vs. standard therapy: 5.8% [95% CI: 2.4 to 11.6]).[2]

Patient-reported outcomes (PROs) were measured using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30), Quality of Life Head and Neck module (QLQ-H&N35) and EuroQol five dimensions questionnaire (EQ-5D-3L) scales. The minimal important differences (MID) for the EORTC QLQ-C30 and the QLQH&N35 scales was a change in ±10 point from baseline while the MID for the EQ-3D-5L visual analog scale was a change in 7 points.[2] Overall, in the nivolumab group, the reported PROs suggest that quality of life is at least maintained for these patients. There was a minimally important decline in painkiller use reported at weeks 9, 15 and 21 and a minimally important increase in weight gain reported at weeks 9 and 15 in the EORTC QLQH&N35.[4] In contrast, there were a number of reported minimally important declines and improvements in the standard therapy group.[4] However, it is unclear whether this variability is related to the treatment or limited sample size at the different assessment periods.

Harms

In CheckMate 141, grade 3 to 4 treatment related adverse events were less frequent in the nivolumab compared to the standard therapy group (13.1% vs. 35.1%).[2] At the time of the interim analysis, two patients in the nivolumab arm died due to treatment-related pneumonitis hypercalcemia, and one patient in the standard therapy arm died due to treatment-related lung infection.[2]

Limitations

- Checkmate 141 was an open-label RCT design. A double-blinded design would have been very difficult to implement due to the assignment of chemotherapy agents. The assessment of overall survival will not be influenced by the open-label nature of the trial because it is an objective outcome. However, more subjective outcomes, such as disease progression or PROs, may be biased in favour of nivolumab.

- In the standard therapy arm, patients were randomized to methotrexate (43%), docetaxel (45%) and cetuximab (12.4%).[2] Although methotrexate and docetaxel have been approved for the treatment of SCCHN in Canada, cetuximab has not been approved or available in Canada. In addition, a subgroup analysis demonstrated a greater benefit of nivolumab as compared to cetuximab (HR: 0.47, 95% CI: 0.22 to 1.01), which may bias the results in favour of nivolumab.[2] It should be noted that only 15 patients were treated with cetuximab in the trial, and since the effect estimates were similar to docetaxel and methotrexate, the impact was considered minimal.

- The Submitter reported that the effect of immunotherapies may not be adequately represented by antitumour activity measures because of pseudoprogression, where tumour response differs for these therapies as compared to chemotherapy.

- Although there was a significant treatment effect for overall survival, the Kaplan-Meier plots for the two treatment arms cross each other.[2] This may increase the uncertainty in the effect estimates as it suggests the hazard for death is not constant over time. Qualitatively, the overall analyses favour nivolumab over standard therapy, but there is uncertainty associated with the actual effect size.

Table 1: Highlights of key outcomes in the Checkmate 141 Trial

Treatment Groups	Nivolumab N = 240	Standard therapy N = 121
Primary Outcome - Overall Survival[A]		
No. deaths (%)	133 (55.4)	85 (70.2)
Median OS, months (95% CI)	7.5 (5.49, 9.10)	5.1 (4.04, 6.05)
OS rate, 12 months (95% CI)	36.0 (28.5, 43.4)	16.6 (8.6, 26.8)
Hazard ratio (97.73% CI; p-value)	0.70 (0.51, 0.96); P = 0.01	
Key Secondary Outcome - Progression Free Survival[B]		
No. PFS events (%)	190 (79.2)	103 (85.1)
Median PFS months (95% CI)	2.04 (1.91, 2.14)	2.33 (1.94, 3.06)
Hazard ratio (95% CI; p-value)	0.89 (0.70, 1.13); P = 0.324	
Key Secondary Outcome - Objective Response Rate[C]		
No. ORR events (%)	32	7
ORR% (95% CI)	13.3 (9.3, 18.3)	5.8 (2.4, 11.6)
Exploratory outcomes		
Time to Response[D], median time to response in weeks (range)	2.1 (1.8, 7.4)	2.0 (1.9, 4.6)
Duration of Response[E], median duration in months (range)	NA	NA

Abbreviations: CI - confidence interval; NA - not available; PFS - progression-free survival; OS - overall survival.

Notes:
A: Time from date of randomization to date of death due to any cause.
B: Time from date of randomization to date of PD per BIRC or death due to any cause.
C: Defined as the sum of complete plus partial responses.
D: Time from date of randomization to date of in documented complete or partial response in patients with confirmed complete or partial response.
E: Time from date of documented complete or partial response in patients to the date of PD or death to any cause with confirmed complete or partial response.
Source: Nivolumab Module 2.5[5]; Ferris et al, (2016). NEJM.[2]

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

From a patient's perspective, pain or discomfort, fatigue, trouble swallowing, sleep deprivation, depression affect their quality-of-life and the ability to enjoy life. As such, trouble swallowing, dry mouth, pain or discomfort, teeth problems, and fatigue are important symptoms of head and neck cancer that are most important to control for patients. Therapies for head and neck include: cisplatin, radiotherapy + cetuximab, paclitaxel, carboplatin, carboplatin + paclitaxel, cisplatin + 5 FU (Fluorouracil), and cetuximab. Common side effects of current therapies include: fatigue, loss of appetite, hair loss, and constipation. Other reported side effects include: nausea, hypothyroidism, peripheral neuropathy, low blood count, trismus, and infection. Patient respondents indicated that they would like nivolumab to: reduce side effects from current medications/treatments, stop disease progression, better control symptoms, and have ease of use. According to Canadian Cancer Survivor Network, patients struggling with disease progression and uncertainly about the future are willing to tolerate fairly significant side effects.

Provincial Advisory Group (PAG) Input

Input was obtained from all nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. PAG identified the following as factors that could impact the implementation on nivolumab for Squamous Cell Carcinoma of the Head and Neck (SCCHN):

Clinical factors:

- Indication creep into first line setting and other types of head and neck cancers

Economic factors:

- Indefinite treatment duration

Registered Clinician Input

Input was not provided by registered clinicians

Summary of Supplemental Questions

There were no supplemental questions identified for this review

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>
<tr><th>Domain</th><th>Factor</th><th>Evidence[2]</th><th>Generalizability Question</th><th>CGP Assessment of Generalizability</th></tr>
<tr><td rowspan="2">Population</td><td>Performance Status</td><td>The majority of patients had an ECOG of 1 (78.4%)
<table><tr><th>ECOG</th><th>Nivo (N = 240)</th><th>ST (N = 121)</th></tr><tr><td>0</td><td>49 (20.4)</td><td>23 (19.0)</td></tr><tr><td>1</td><td>189 (78.8)</td><td>94 (77.7)</td></tr><tr><td>2</td><td>1 (0.4)</td><td>3 (2.5)</td></tr><tr><td>Not reported</td><td>1 (0.4)</td><td>1 (0.8)</td></tr></table></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>Clinicians would consider the results generalizable to ECOG 2 patients but not to patients ECOG 3 or higher.

Although only a few patients with ECOG 2 were enrolled and reported experience with nivolumab, its favorable toxicity profile reported in the RCT, and the inclusion of some patients with ECOG 2 in the RCT influenced the CGP who felt it would be a reasonable option for ECOG 2 patients who are still ambulatory to some degree but poor candidates for chemotherapy. Clinicians would like to have treatment to offer to ECOG 3 patients who are usually not considered suitable for drug treatment, and a trial of nivolumab would likely be safe. However, as these patients are known to have shorter survival, the CGP felt that generalizing to them would be reaching further than the RCT data allowed</td></tr>
<tr><td>Age</td><td>The average age of patients in the trial was 60 years of age
<table><tr><th>Age</th><th>Nivo (N = 240)</th><th>ST (N = 121)</th></tr><tr><td>Median Age, (range)</td><td>59 (29–83)</td><td>61 (28–78)</td></tr><tr><td>≥75 years, n (%)</td><td>12 (5.0)</td><td>6 (5.0)</td></tr></table></td><td>Does the age restriction in the trial limit the interpretation of the trial results with respect to the target population?</td><td>Other than being age 18 years or older, age was not restricted in this trial, and the results are considered generalizable to all adult patients.</td></tr>
</table>

	Organ dysfunction	Inclusion criteria for the trial: Screening laboratory values must meet the following criteria (using CTCAE v4) and should be obtained within 14 days prior to randomization: i) WBC ≥ 2000/µL ii) Neutrophils ≥ 1500/µL iii) Platelets ≥ 100 x103/µL iv) Hemoglobin ≥ 9.0 g/dL v) Serum creatinine £ 1.5 x ULN or creatinine clearance (CrCl) > 40 mL/min (using the Cockcroft-Gault formula) vi) AST/ALT ≤ 3 x ULN vii)Total Bilirubin ≤ 1.5 x ULN (except subjects with Gilbert Syndrome, who can have total bilirubin < 3.0 mg/dL). viii) Calcium levels must be normalized and maintained within normal limits for study entry and on treatment. Medical management of calcium levels is permitted. Note: Normal calcium levels may be based on ionized calcium or adjusted for albumin. ix) Subjects with an initial magnesium < 0.5 mmol/L (1.2 mg/dL) may receive corrective magnesium supplementation but should continue to receive either prophylactic weekly infusion of magnesium and/or oral magnesium supplementation (eg, magnesium oxide) at the investigator's discretion.	Does the exclusion of patients with organ dysfunction limit the interpretation of the trial results with respect to the target population (e.g., Canadian clinical practice,	The typical restrictions around organ function due not limit the generalizability of these results. Patients with HIV and known hepatitis B or C infection were excluded. The CGP agreed that the trial results were considered generalizable to patients with these infections provided their infection was under control and treatment decision was at the discretion of the treating physician. As nivolumab may induce autoimmune effects it is considered contraindicated in patients with organ allografts requiring immunosuppression, and relatively contraindicated in patients with active autoimmune and inflammatory conditions. RCTs are carefully designed to show effectiveness of a new therapy compared to standard and provide a basis for regulatory approval. There is very little evidence that the specific antitumor immune effects of nivolumab result in worsening of these chronic viral infections if they are under medical control. To the contrary there is emerging evidence that such treatment may be quite safe. The CGP felt that most patients in this situation would accept the potential risks of nivolumab treatment, therefore use of nivolumab in this situation should be an individualized decision based on a discussion between the patient and their oncologist.

<table>
<tr>
<td></td>
<td>Metastatic Sites</td>
<td>Patients were excluded if they had
• active brain metastases
• histologically confirmed recurrent or metastatic carcinoma of the nasopharynx, squamous cell carcinoma of unknown primary, and salivary gland or non-squamous histology.</td>
<td>Did the exclusion of patients with certain sites of metastatic disease limit the interpretation of the trial results with respect to the target population (e.g., Canadian clinical practice, patients without the factor, etc.)?</td>
<td>The trial results are not generalizable to patients with active brain metastases, EBER-positive nasopharyngeal cancer, salivary gland cancers, or tumours of non-squamous histology.

The trial results are generalizable to patients with treated and controlled brain metastases, EBER-negative nasopharyngeal cancers and head and neck squamous cell cancers of unknown primary. The CGP cited the similar tumor biology, clinical behavior and identical treatment as mucosal SCCHN for these other histologies. The CGP also noted that brain metastases are rare in RMSCCHN. If treated and controlled the CGP felt it would be quite reasonable to offer nivolumab therapy.</td>
</tr>
<tr>
<td></td>
<td>Biomarkers</td>
<td>The trial identified two biomarkers: 1) PD-L1 and 2) HPV 16.
<table>
<tr><th></th><th>Nivolumab n (%)</th><th>STD, n(%)</th><th>Unstratified HR (95% CI)</th></tr>
<tr><td>All patients</td><td>240 (100.0)</td><td>121 (100.0)</td><td>0.69 (0.53–0.91)</td></tr>
<tr><td>PD-L1 expression level</td><td></td><td></td><td></td></tr>
<tr><td>≥1%</td><td>88 (36.7)</td><td>61 (50.4)</td><td>0.55 (0.36–0.83)</td></tr>
<tr><td>≥5%</td><td>54 (22.5)</td><td>43 (35.5)</td><td>0.50 (0.30–0.83)</td></tr>
<tr><td>≥10%</td><td>43 (17.9)</td><td>34 (28.1)</td><td>0.56 (0.31–1.01)</td></tr>
<tr><td><1%</td><td>73 (30.4)</td><td>38 (31.4)</td><td>0.89 (0.54–1.45)</td></tr>
<tr><td><5%</td><td>107 (44.6)</td><td>56 (46.3)</td><td>0.81 (0.55–1.21)</td></tr>
<tr><td><10%</td><td>118 (49.2)</td><td>65 (53.7</td><td>0.73 (0.50–1.06)</td></tr>
<tr><td>Not quantifiable</td><td>79 (32.9)</td><td>22 (18.2)</td><td>0.79 (0.44–1.44)</td></tr>
<tr><td>p16 status</td><td></td><td></td><td></td></tr>
<tr><td>Positive</td><td>63 (26.2)</td><td>29 (24.0)</td><td>0.56 (0.32–0.99)</td></tr>
<tr><td>Negative</td><td>50 (20.8)</td><td>36 (29.8)</td><td>0.73 (0.42–1.25)</td></tr>
</table>
</td>
<td>Is the biomarker an effect modifier (i.e., differences in effect based on biomarker status)? Are the results of the trial applicable to all subgroups equally? Is there a substantial group of patients excluded from the trial to whom the results could be generalized?</td>
<td>There is no convincing evidence that either of the biomarkers (PD-L1 and HPV 16) is an effect modifier. The trial results are equally applicable to all subgroups. No substantial group of patients has been excluded from the trial.</td>
</tr>
</table>

<table>
<tr><td>Intervention</td><td>Line of therapy</td><td>Patients with recurrent squamous-cell carcinoma of the head and neck whose disease had progressed within 6 months after platinum-based chemotherapy to receive nivolumab (at a dose of 3 mg per kilogram of body weight) every 2 weeks or standard, single-agent systemic therapy (methotrexate, docetaxel, or cetuximab).</td><td>Are the results of the trial generalizable to other lines of therapy?</td><td>Over 50% of patients in the trial had more than 1 line of prior chemotherapy. Therefore the trial results are generalizable to patients who have had more than one line of prior chemotherapy</td></tr>
<tr><td rowspan="2">Comparator</td><td>Standard of Care</td><td>Methotrexate and docetaxel have been approved in Canada for the treatment of SCCHN while cetuximab has not been approved.
<table><tr><th></th><th>Nivolumab n (%)</th><th>STD, n(%)</th><th>Unstratified HR (95% CI)</th></tr><tr><td>All patients</td><td>240 (100)</td><td>121 (100)</td><td>0.69 (0.53–0.91)</td></tr><tr><td colspan="3">Intended standard therapy</td><td></td></tr><tr><td>Cetuximab</td><td>33</td><td>15</td><td>0.47 (0.22–1.01)</td></tr><tr><td>Methotrexate</td><td>119</td><td>52</td><td>0.64 (0.43–0.96)</td></tr><tr><td>Docetaxel</td><td>88</td><td>54</td><td>0.82 (0.53–1.28)</td></tr></table></td><td>If the comparator is non-standard, are the results of the trial applicable in the Canadian setting?

Yes applicable, effect of cetuximab modest due to small population receiving this treatment.</td><td>Cetuximab is not approved or funded for this indication in Canada. However, the proportion of patients receiving cetuximab in the control arm is small (12.3%). By excluding these patients the hazard ratio remains similar (0.73), so the results remain generalizable.</td></tr>
<tr><td>Dose and Schedule</td><td>Patients in Checkmate 141 were treated with one of the following regimens:
Nivolumab: 3 mg/kg intravenous (IV) dose of nivolumab every two weeks.
Cetuximab: 400 mg/m^2 IV dose of cetuximab followed by 250 mg/m^2 weekly
Methotrexate: 40 mg/m^2 IV dose of methotrexate weekly
Docetaxel: 30 mg/m^2 IV dose of docetaxel weekly</td><td>If the dose and/or schedule is not standard, are the results of the trial relevant in the Canadian setting?</td><td>The nivolumab and methotrexate doses are standard in Canada. Docetaxel may also be given on a schedule of 75 mg/m^2 IV q3weeks. This schedule difference has no influence on generalizability of the trial results.</td></tr>
<tr><td>Outcomes</td><td>Assessment of Key Outcomes</td><td>Are the key outcomes assessed differently in the trial compared with clinical practice in Canada?</td><td>If the trial used a different method of assessment than that used in Canadian clinical practice, are the results of the trial applicable to the Canadian setting?</td><td>The method of assessment is the same as that used in Canadian clinical practice, other than that HRQoL data would usually not be collected.</td></tr>
</table>

1.2.4 Interpretation

Burden of Illness and Need

Although it is expected that 1,600 Canadians will suffer and die due to recurrent and metastatic squamous cell carcinoma of the head and neck (RMSCCHN) this year, there is sparse high-level evidence that any currently funded anticancer drug therapies are clinically beneficial.

Multiple randomized controlled trials (RCTs) studying cytotoxic drugs have shown improved ORRs with combination chemotherapy compared to single agent treatment in the 1st-line setting; but toxicity to patients was higher, overall survival was not improved, and HRQoL poorly studied. Only the addition of the anti-EGFR monoclonal antibody, cetuximab, to platinum-based combination chemotherapy has been demonstrated to improve overall survival;[6] however, toxicity was increased, and cetuximab has neither regulatory approval nor public funding in Canada for this indication.

Sparser still is high-level evidence supporting effective treatment for RMSCCHN patients whose cancers progress on or after 1st-line chemotherapy. Docetaxel was shown to have a superior response rate compared to methotrexate in a small randomized phase 2 trial supporting the use of taxanes in this setting.[7] Despite at least 4 negative RCTs comparing anti-EGFR small molecules or monoclonal antibodies with chemotherapy, from an internationally perspective, cetuximab is still considered a therapeutic option in the 2nd-line setting based on ORRs in uncontrolled trials. Cetuximab is however not routinely available in Canada nor does it have regulatory approval in this setting. Due to lack of convincing evidence for best practice, there is practice variability and docetaxel, paclitaxel, methotrexate and fluoropyrimidines are all commonly used. Although not reimbursed by jurisdictions, cetuximab is reasonable to consider for patients who have private insurance. Other than immune checkpoint inhibitors, only the PI3 kinase inhibitor buparlisib in combination with paclitaxel has shown any promise of activity in this setting.[8]

Effectiveness

From this perspective the results of the Checkmate 141 RCT are compelling. The most important result of the Checkmate 141 RCT was the observation that patients receiving nivolumab lived longer on average that patients receiving investigator s' choice chemotherapy. The risk of death was reduced by 30% during the trial observation period (HR: 0.70, p=0.01) but even more impressive was a doubling in the number of patients alive at 1 year from 16.6% to 36.0%, suggesting that the survival benefit was durable. Allowing for limitations due to patient drop out, HRQoL measured using the QLQ-C30 and QLQ-H&N35 appeared to be preserved in patients receiving nivolumab and deteriorated in patients on the control arm reaching statistical significance in several domains at weeks 9 and 15. Supportive of enhanced tumor control with nivolumab was a doubling of the objective response rate (ORR) at 13.3% (versus 5.8%) although this did not achieve statistical significance. Improvements in these endpoints are all highly relevant to patients.

Safety

Severe adverse effects (grade 3 or higher) were nearly one-third less common with nivolumab than with single agent chemotherapy, occurring in 13.1% of nivolumab patients. The most common severe adverse effects with nivolumab were fatigue (2.1%) and anemia (1.3%). Overall the most common adverse effects of any severity occurring in over 5% of patients were: fatigue (14.0%), nausea (8.5%), rash (7.6%), decreased appetite (7.2%),

pruritus (7.2%), diarrhea (6.8%) and anemia (5.1%). Except for rash, pruritus, and decreased appetite, all of these occurred more frequently in the chemotherapy control arm patients. Three treatment-related deaths occurred: two with nivolumab and one with chemotherapy. Reduced treatment toxicity is highly relevant to patients. The observation of a higher ORR with less toxicity is unique among RMSCCHN RCTs.

Limitations and Generalizability

Enrollment was limited to patients with RMSCCHNs of the conventional mucosal sites who had progressed within 6 months of chemotherapy and were of good performance status (ECOG 0 or 1). All patients had at least one line of prior chemotherapy but 54.5% had two or more prior lines of systemic therapy. The Clinical Guidance Panel thought these data were generalizable to patients with squamous cell carcinomas of less common mucosal sites that were not included in the trial, such as the nasal cavity and paranasal sinuses, and EBER-negative nasopharyngeal cancer, but not to primary skin cancers. As well, the favorable safety profile suggested that nivolumab was a reasonable choice in patients with ECOG 2 performance status.

Although the Checkmate 141 trial required evidence of cancer progression within 6 months from prior treatment, the Clinical Guidance Panel agreed that ascertainment of this time frame was not critical in this patient population and should not be used as a requirement for eligibility to receive nivolumab. The median progression-free survival for RMSCCHN patients after 1st-line chemotherapy is 3.3 months (95% CI, 2.9-4.3),[6] confirming that virtually all patients have progression within 6 months of 1st-line treatment. As well, tumor progression within this time frame is not routinely used to make treatment decisions and might be difficult to ascertain in real world practice, and requiring this for nivolumab eligibility would impose a burden of additional CT scanning on patients. The CGP further noted that the criteria of being "platinum-refractory" is probably an irrelevant term in this population. Firstly, the CGP note that RMSCCHN is not sufficiently platinum-sensitive to begin with. For example, objective response rates in the best modern studies using platinum combinations in the first-line setting is only about 25%.[9] This distinguishes it from other cancer types (e.g. ovarian cancer, germ cell cancer, urothelial cancer, or small cell lung cancer) where platinum-sensitivity and retreatment is logical and a clinical reality. Secondly, virtually all RMSCCHN patients progress within 6 months of starting platinum-based chemotherapy. For example, in the SPECTRUM RCT of cisplatin/fluorouracil +/- panitumumab in RMSCCHN (n=657), PFS in the control arm was 4.6 months (95% CI, 4.1–5.4 months).[9] In real world practice the PFS is likely to be even shorter. Thirdly, most patients will be heavily platinum exposed by the time they reach 2nd-line treatment for RMSCCHN. Most would have received cisplatin with RT as initial therapy, then will have received platinum as 1st-line therapy for RMSCCHN. So even if they progress after 6 months (rare) it is unlikely they will be able to receive further cisplatin due to cumulative cisplatin exposure and its toxicities (neuropathy, nephropathy, etc). Carboplatin substitution for such a patient does not make sense as carboplatin is known to be a less effective drug than cisplatin in this disease, and so is not an adequate substitute for "platinum re-challenge" in a cisplatin-experienced RMSCCHN population. Following the posting on the pERC initial recommendation specifying the use of a 6 month cutoff (recurrence within six months of potentially curative therapy or after receiving platinum-based therapy in a non-curative setting) for eligibility of treatment in some patients, the submitter provided feedback on the relevance of such a cutoff. The CGP considered the feedback and reiterated that the use of a 6 month cutoff is unlikely to impact the eligibility of patients as it is rarely used in clinical practice and virtually all patients have progression within 6 months of 1st-line treatment. The CGP agreed that it is uncommon for patients to progress after 6 months. In these uncommon instances, the CGP agreed that patients could be carefully re-treated

with platinum based chemotherapy (eg, paclitaxel/carboplatin). Progression after this would render patients eligible for nivolumab treatment. The CGP however note that there may be patients who's "potentially curative therapy" may have only been surgery and/or RT (i.e. these patients would not have received chemotherapy at all). Therefore specifying that recurrence within six months of curative therapy may result in nivolumab treatment of entirely chemo naïve patients. The CGP agreed that the availability of nivolumab in patients who are ineligible for chemotherapy is reasonable only in some patients. This would include patients with severe liver disease or myelodysplastic syndromes, etc., patients who should not be exposed to cytotoxic drugs. Patients with solid organ transplant are another category of patients ineligible for chemotherapy but they are contraindicated for treatment with nivolumab. Intolerance of first line chemotherapy for RMSCCHN as a basis for funding is more difficult, and is beyond the data provided by the trial. Usually chemotherapy such as paclitaxel/carboplatin is reasonably tolerated even in elderly/sicker patients if dosed appropriately. Ideally a case-by-case review for eligibility of patients may be important to determine patients who are ineligible or truly intolerant to chemotherapy.

The submitter also commented on the relevance of cetuximab as a comparator in the Canadian setting. The reference provided by the submitter in the feedback to support this claim is speaking to the use of cetuximab in the first line setting as an alternative to chemotherapy. In the second line setting, which is of relevance to the current review, cetuximab is not funded by jurisdictions neither does it have regulatory approval.

Lastly, the submitter questions analysis conducted by the economic guidance panel with regards to the expected long term survival of patients. The CGP noted that in first line trials of platinum-cased combination chemotherapy +/- cetuximab (Vermorken 2008 NEJM), less than 20% of patients were alive after 24 months. Given that these patients do not fully represent the clinical population (patients on trial had good performance status/normal organ function etc.), the CGP agreed that the survival of patients encountered in the clinical setting is expected to be even less. Based on this data, the CGP agree that using a more conservative estimate for survival in the second line setting is reasonable.

The trial design was pragmatic in that it allowed investigators' choice of control arm chemotherapy consisting either of docetaxel, methotrexate or cetuximab. These are considered reasonable standard treatment options. However, as cetuximab is not routinely available in Canada for this indication, this specific agent lacks relevance. As well, nivolumab benefit was greater compared to cetuximab in subgroup analyses (HR: 0.47) potentially biasing results more favorably toward nivolumab than would be expected in a Canadian population. However, as the results were qualitatively similar with docetaxel and methotrexate, and only 12.4% of control patients received cetuximab, the Clinical Guidance Panel considered the impact of this on the results to be minimal.

The strengths of the trial included the selection of overall survival as the primary endpoint, collection of HRQoL data (a rarity in RMSCCHN RCTs), and the fact that treatment crossover at progression was not allowed after the study closure. A common practice in oncology trials but a weakness of the trial design was the lack of blinding of investigators and patients to treatment received. This raises potential for ascertainment bias that could lead to earlier discontinuation of chemotherapy compared to nivolumab. Often patients receiving immune checkpoint inhibitor therapy who are clinically well are continued on treatment despite evidence of tumor growth on imaging due to the possibility of "pseudoprogression" from tumor inflammation; whereas chemotherapy patients would always have treatment discontinued. The CGP considered the potential effect of this on the results uncertain. Clinical practice is evolving in this area, and

recently new guidelines for assessing tumor response in patients receiving immunotherapy have been developed.[10]

Overall survival was analyzed for differential benefits by tumour PD-L1 expression or tumour p16 status. The Clinical Guidance Panel did not consider the results of these biomarker analyses convincing in identifying a subgroup of patients who would not benefit from a trial of nivolumab therapy. Therefore, the Clinical Guidance Panel did not support use of nivolumab based on tumor PD-L1 or p16 expression.

This was an international RCT that included Canadian participants, enhancing its generalizability. The study would have been conducted mainly in academic centres, but the Clinical Guidance Panel did not consider this a limitation due to the widespread adoption of nivolumab as treatment for other cancer indications common in community practice. Nivolumab should be prescribed by clinicians knowledgeable about its autoimmune adverse effects, and clinicians supervising these patients should be alert to the spectrum of these effects and their treatment.

The Checkmate 141 trial required patients to have progressive disease after 1st-line platinum-based chemotherapy. The Clinical Guidance Panel considered it very unlikely that patients would be switched early after 1st-line chemotherapy to access nivolumab. The median duration of 1st-line chemotherapy treatment is 12 weeks (IQR, 6 to 19).[6] This suggests that patients with progressive disease despite 1st-line chemotherapy are usually obvious after 2 cycles of chemotherapy. As there is no guarantee that nivolumab will be effective for any patient, patients responding to 1st-line chemotherapy would usually continue this until maximum benefit was achieved. In rare circumstances, first-line chemotherapy may produce extreme toxicities in patients despite optimal supportive care. Thus the CGP felt that it is reasonable that these patients may be considered for nivolumab at the time their disease progresses. However, the CGP agreed that there is currently no available evidence to support the use of nivolumab in patients who are currently undergoing first-line therapy.

It is likely that a minority of nivolumab-treated patients would be candidates for 3rd-line chemotherapy, and typically the drugs currently used in 2nd-line would be considered. Very few patients without response to nivolumab would be expected to be suitable candidates for subsequent chemotherapy. Those patients who benefit from nivolumab represent a novel clinical group, and it is likely that a substantial proportion of these patients would be suitable for further chemotherapy when their cancer progress. However, the effectiveness of standard agents in this group is uncertain and likely very modest.

1.3 Conclusions

The Clinical Guidance Panel concluded that there is a net clinical benefit to nivolumab in the treatment of recurrent and/or metastatic squamous cell carcinoma of the head and neck with evidence of cancer progression after at least one line of prior platinum-based chemotherapy based on one high-quality randomized controlled trial that demonstrated a clinically and statistically significant benefit in overall survival and HRQoL for nivolumab compared with investigators' choice of docetaxel, methotrexate, or cetuximab. Adverse event profiles were better for nivolumab than control chemotherapy.

In making this conclusion, the Clinical Guidance Panel also considered that:

- These results generalizable to patients with treated and controlled brain metastases, mucosal squamous cell carcinomas arising from any head and neck subsite regardless of

HPV status (except EBER-positive nasopharyngeal cancer and primary skin cancers), patients with performance status ECOG 2, and those with multiple lines of prior chemotherapy.

- Patients with HIV and known hepatitis B or C infection were excluded from the trial. The CGP agreed that the trial results were considered generalizable to patients with these infections provided their infection was under control and treatment decision was at the discretion of their treating physician. As nivolumab may induce autoimmune effects it is considered contraindicated in patients with organ allografts requiring immunosuppression, and relatively contraindicated in patients with active autoimmune and inflammatory conditions.
- There is not convincing evidence that either of the biomarkers (PD-L1 and HPV 16) is an effect modifier. The trial results are equally applicable to all subgroups.

2 BACKGROUND CLINICAL INFORMATION

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

2.1 Description of the Condition

In 2016, over 5,700 Canadians were diagnosed with squamous cell carcinoma of the head and neck (SCCHN) and 1,600 died from it. (Canadian Cancer Society website) In the US, SEER registry information indicates that 32% of SCCHN patients are diagnosed with localized disease, 44% with regionally advanced disease and 18% distant metastases. (SEER website) Of the patients with lymph node involvement who are at highest risk of recurrence, the progression-free survival at 3 years is estimated to be 38% in carcinogen-associated cancers and 74% in human papilloma virus (HPV)-related cancers when treated with concurrent chemoradiation.[11] Therefore, a significant proportion of SCCHN patients will present with or develop metastatic disease and will require further therapy. While SCCHN represents a small proportion of total cancer diagnoses in Canada, it is associated with significant morbidity due to its anatomical location and effective treatment options are necessary.

SCCHN is now recognized to be comprised of two distinct entities: primarily carcinogen-induced disease related to smoking, alcohol and direct toxin exposure that typically involves the oral cavity, larynx and hypopharynx; and HPV-related disease that usually presents as oropharyngeal cancer involving the base of tongue or tonsil. The incidence of SCCHN is increasing largely attributable to an increase in HPV-related oropharyngeal cancer. From 1992 to 2012 HPV-related SCCHN has increased by 56% in men and 17% in women. (Canadian Cancer Society 2016) The impact of HPV vaccination strategies will not be seen for years given the long latency period before disease development.

2.2 Accepted Clinical Practice

Recurrent and metastatic squamous cell carcinoma of the head and neck (RMSCCHN) poses a treatment challenge due to limited therapeutic options. Local recurrence is often associated with significant morbidity owing to the functional location of the disease. Here, tumours often impede with eating swallowing and even breathing. Furthermore, these tumours may also be bulky, ulcerated, leading and super infected. As a result, patients may become quite debilitated because of the failure to intake adequate nutrition. Due to the debility associated with these local recurrences, patients' performance status may be quite poor and they are often intolerant of cisplatin- based systemic chemotherapy..[12] The reason for this is likely multifactorial. The toxicity and relatively low efficacy of 1st-line chemotherapy in RMSCCHN is not particularly appealing to many patients who decline treatment. Referral patterns contribute as well, as surgeons or radiation oncologists are typically the first contact for newly diagnosed patients, and they may decide not to refer a patient or the patient may decline the referral. There are patients seen by medical oncologists who are not be considered suitable candidates for chemotherapy due to their medical status as well. Salvage surgical resection and/or re-irradiation are usually considered but are often not feasible. Use of palliative radiation may be limited due to prior high dose curative intent radiotherapy earlier in the course of disease management.

For RMSCCHN, phase II trials of single agent chemotherapy drugs have demonstrated a superior response rate and suggested a survival benefit with cisplatin compared to bleomycin or methotrexate, the standard of care since the 1950s.[13,14] Subsequently,

cisplatin became the backbone of doublet chemotherapy. However, although response rates and toxicity risks differ, no chemotherapy regimens have clearly demonstrated a survival benefit compared to methotrexate in adequately powered randomized trials (RCTs). Recent analyses of these RCTs suggest that the efficacy of first-line chemotherapy may be less than anticipated, likely due to patient selection and more aggressive initial curative treatment, and there is no evidence of health-related quality of life benefits.[15] In 2008, a RCT of first-line platinum/fluorouracil (5-FU) with and without cetuximab in RMSCCHN demonstrated an improvement in median survival from 7.4 to 10.1 months (HR 0.8, 95% CI 6.4 to 8.3 p=0.04) with the addition of EGFR-directed therapy.[6] This has been the only adequately powered RCT of first-line drug treatment for RMSCCHN to report an overall survival benefit. However, cetuximab is not approved or funded in Canada for this indication; therefore, a platinum-based chemotherapy doublet alone remains standard first-line treatment. Typically carboplatin/paclitaxel or cisplatin/5-FU are used in clinical practice in Canada, on the basis of a phase III RCT that compared those two treatment options that demonstrated no significant differences in overall survival or response rates.[16] Single agent cisplatin, methotrexate, capecitabine or docetaxel are options considered for patients unsuitable for doublet chemotherapy.

Due to a lack of convincing evidence, there is practice variability in establishing a best practice in the management of recurrent or metastatic SCCHN. For instance, docetaxel, paclitaxel methotrexate and fluoropyrimidines are commonly used. Indeed, one randomized phase II trial showed that docetaxel had a superior response rate compared to methotrexate.[7] Furthermore, capecitabine and paclitaxel with or without carboplatin may also be considered but on the basis of limited evidence.[17] However, in some jurisdictions cetuximab may be used in Canada but it is not usually provided to patients because it does not have regulatory approval for these cancers.

2.3 Evidence-Based Considerations for a Funding Population

Treatment with immune checkpoint inhibitors (ICIs) of PD-1 or PD-L1 in SCCHN represents a logical choice. Genomic mutational burden is high in these cancers and is similar with other disease sites in which checkpoint inhibition is effective, such as melanoma and non-small cell lung, renal cell and bladder cancers. In HPV-related SCCHN it has been observed that PD-L1 is up-regulated suggesting that this subtype of disease represents a virally-induced failure of the immune system potentially modulated by immunotherapy. As a result, ICIs have been studied in RMSCCHN in a number of clinical trials.

A single-arm phase II study evaluated pembrolizumab (PD-1 inhibitor) 200 mg IV every 3 weeks in RMSCCHN patients previously treated with platinum and cetuximab. The preliminary results showed a median OS of 8 months in patients with greater than 6 months of follow-up.[18] In a phase Ib study, the combined initial cohort (pembrolizumab 10 mg/kg IV every 2 weeks, n=60) and expansion cohort (200 mg IV every 3 weeks, n=132) had a median OS of 8.5 months in a heavily pretreated population.[19] Durvalumab, a PD-L1 inhibitor, was evaluated in a phase I/II expansion cohort that included 62 RMSCCHN patients. A response rate of 11% and a median OS of 8.9 months were reported.[20] Consistently with all of the ICIs studied (nivolumab, pembrolizumab and durvalumab), while tumour response rate and PFS have remained unimpressive, the median OS has ranged from 7-8 months (regardless of number of prior therapies) representing a significant improvement over the standard treatments used or historical controls.

The topic of this review is a phase III study, Checkmate 141, which compared the PD-1 inhibitor nivolumab at a dose of 3 mg/kg IV every 2 weeks to standard of care chemotherapy (investigators choice of: methotrexate 40-60 mg/m² IV weekly, docetaxel

30-40 mg/m² IV weekly, or cetuximab 400 mg/m² IV once then 250 mg/m² weekly) in previously treated RMSCCHN.[2] The trial design had a planned sample size of 360 patients but was stopped early with overall survival and health-related quality of life benefits reported.

2.4 Other Patient Populations in Whom the Drug May Be Used

Nivolumab has been approved for use in Canada for the treatment of multiple cancer types including melanoma, non-small cell lung cancer and renal cell carcinoma. The US FDA has also approved nivolumab for use in relapsed or progressed Hodgkin lymphoma, and has approved other ICIs in non-small cell lung cancer and urothelial carcinoma. In Checkmate 141 the inclusion criteria included histologically confirmed RMSCCHN (oral cavity, pharynx, larynx) not amenable to curative therapy and good performance status. Patients with non-squamous histologies (i.e. those with salivary gland tumors) and patients with nasopharyngeal carcinoma were excluded from study. Notably, these disease sub-sites are independent areas of clinical research, with clinical trials open to accrual. Patients were required to have tumour progression or recurrence within 6 months of last dose of platinum therapy (i.e. platinum-refractory) in either the definitive treatment or first-line non-curative setting. Exclusion criteria included patients with active, known or suspected auto-immune disease, acute/chronic hepatitis infection, and patients with a condition requiring systemic treatment with either corticosteroids (>10 mg daily prednisone equivalents) or non-steroid immunosuppressive therapy. In clinical practice, immunotherapy is well tolerated and it is likely patients with RMSCCHN from other sites in the head and neck not included in the RCT (e.g. paranasal sinuses), those with lesser performance status, and those with recurrence beyond 6 months after cisplatin might be considered for nivolumab therapy.

3 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

Canadian Cancer Survivor Network (CCSN) provided input on nivolumab (Opdivo) for the treatment of recurrent or metastatic squamous cell cancer of the head and neck (SCCHN) after platinum-based therapy in adults. Their input is summarized below.

The information used to complete sections 3.1 Condition and Current Therapy Information and 3.2 Information about the Drug Being Reviewed was obtained through a survey conducted by CCSN in January/February 2016 on Survey Monkey. The survey was publicized on CCSN's website (survivornet.ca), social media feeds (Facebook and Twitter) and in a CCSN e-letter. As well, an email about the survey was circulated to the following 19 head and neck cancer support groups around the world:

- The Support for People with Oral & Head and Neck Cancer (SPOHNC)
- Head and Neck Cancer Support
- Head and Neck Cancer Alliance
- Oral Cancer Foundation
- American Head and Neck Society
- Oral Cancer Awareness Foundation
- Macmillian Cancer Support
- The Swallows Group
- Head and Neck Cancer Foundation
- Merseyside Regional Head and Neck Cancer Centre
- Headstart's Head and Neck Cancer Centre
- Ipswich Head and Neck Support Group
- Colchester Head and Neck Support Group
- About Face
- Cancer Research Centre UK
- Cancer Laryngectomy Trust
- Australian and New Zealand Cancer Society
- Head and Neckers – New Zealand
- Sydney Head and Neck Cancer Institute

A total of 45 respondents participated in the survey (40 head and neck cancer patients and 5 caregivers). None of the respondents had experience with nivolumab.

From a patient's perspective, pain or discomfort, fatigue, trouble swallowing, sleep deprivation, depression affect their quality-of-life and the ability to enjoy life. As such, trouble swallowing, dry mouth, pain or discomfort, teeth problems, and fatigue are important symptoms of head and neck cancer that are most important to control for patients. Therapies for head and neck include: cisplatin, radiotherapy + Cetuximab, paclitaxel, carboplatin, carboplatin + paclitaxel, cisplatin + 5 FU (Fluorouracil), and Cetuximab. Common side effects of current therapies include: fatigue, loss of appetite, hair loss, and constipation. Other reported side effects include: nausea, hypothyroidism, peripheral neuropathy, low blood count, trismus, and infection. Patient respondents indicated that they would like nivolumab to: reduce side effects from current medications/treatments, stop disease progression, better control symptoms, and have ease of use. According to CCSN, patients struggling with disease progression and uncertainly about the future are willing to tolerate fairly significant side effects.

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

Please see below for a summary of specific input received from the patient advocacy groups.

3.1 Condition and Current Therapy Information

3.1.1 Experiences Patients have with Squamous Cell Cancer of the Head and Neck

CCSN asked respondents questions on related to symptoms which affect patients' day-to-day living and quality of life and which symptoms are the most important to patients.

When CCSN asked what symptoms or problems they experienced with head and neck cancer that affected their day-to-day living and quality of life, 43 survey respondents replied:

Symptoms or Problems Experienced	%
Dry mouth	76.74%
Trouble swallowing	69.77%
Pain or discomfort	53.49%
Teeth problems	48.84%
Speech problems	44.19%
Weight loss	41.86%
Fatigue	41.86%
Anxiety	34.88%
Loss of appetite	32.56%
Coughing	27.91%
Depression	27.91%
Financial difficulties	27.91%
Post-traumatic stress	18.60%
Insomnia	16.28%
Dyspnea	11.63%
Shortness of breath	2.33%
Weight gain	0.00%

In addition to the above symptoms/problems reported by CCSN, patient respondents also stated:

- *"I was given drugs to control pain. A feeding tube was installed to help me survive. In spite of that, I still lost 50 pound. I was treated at the University of Pennsylvania in Philadelphia Pennsylvania, USA"*
- *"Could not brush my teeth the same way on each side"*
- *"Nausea"*
- *"slight swelling in my throat"*
- *"Severe neck cramps"*
- *"Trismus"*
- *"I had a horrendous problem with "mucus mouth""*
- *"Fresh blood in the mouth"*
- *"Radio necrosis of left mandible. Reduced blood flood in gum and other tissues in same area. Stiffening of tissues in same area. Loss of almost all taste buds. Total destruction of submandibular salivary glands. Stiffness of tissue in left neck"*

- *"Blisters in mouth from radiation & Burns to skin"*
- *"Need to make accommodations for eating. Mild articulation issues"*
- *"Neuropathy"*
- *"Diplopia (double vision)"*
- *"Loss of feeling in some areas after surgery, especially the neck and shoulder, neck stiffness and difficulty maintaining head and neck posture, neuropathy"*
- *"Choking on stringy mucus and related gagging and vomiting was a problem"*
- *"Went to dentist as I thought my denture was irritating left rear gum area"*
- *"My surgery was 22 years ago Feb. 14. When I was going through treatment also experienced extreme fatigue, loss of appetite, weight loss, burns from cheek bone to collar bone on that side (left). Both inside and outside of neck. Still have coughing too"*

Respondents then rated the top five symptoms that are the most important to control:

Top five symptoms that are the most important to control	%
Trouble Swallowing	72.09%
Dry Mouth	72.09%
Pain or Discomfort	51.16%
Teeth Problems	46.51%
Fatigue:	25.58%

According to CCSN, head and neck cancer patients are both physically and psychologically impacted by living with advanced cancer. CCSN reports that 51.16% of respondents experience pain or discomfort and 41.86% of respondents experience fatigue. As well, a total of 72.09% of respondents experience trouble swallowing and 25.58% of respondents were sleep deprived and experience depression and 18.60% of respondents experience anxiety.

CCSN expressed that all of these problems and issues affect their quality-of-life and the ability to enjoy life.

To illustrate the patients and issues, below are comments from patient respondents:
- *"The neck cramps make it difficult to function at times"*
- *"Thickened saliva was my biggest problem. Over $40,000 in dental bills! Had to have all my teeth crowned"*

3.1.2 Patients' Experiences with Current Therapy for Squamous Cell Cancer of the Head and Neck

CCSN also asked about the management of head and neck cancer including which therapies and treatments patients are currently using to treat their disease; how effective these therapies and treatments have been; which side effects they experienced; and whether patients have had issues accessing current therapies and treatment.

When asked about what treatments patients were using, respondents answered the following:
- Radiotherapy + cisplastin: 7.50%
- Carboplatin + paclitaxel: 2.50%

CCSN noted that many of the respondents were not using the treatments listed and instead commented the following:

- *"I was also treated with radiation 5 days a week for 7 weeks. I was treated 10 years ago and am doing very well"*
- *"Nothing just constant check up with any of my many doctors & dentists"*
- *"Taxol, radiation, immunotherapy (pembrolizumab)"*
- *"Exercises for mouth opening and swallow function - liquid only diet"*
- *"Cancer had metastasized to lung, then joined a Clinical trial with Keytruda (pembrolizumab). Finished trial with complete response (no cancer detected)"*
- *"I am a survivor of 11 years now. I still have problems with dry mouth, chewing my food, choking on water and food and with my teeth (pain) and fibrosis from the radiation I received so I'm not able to open my mouth very wide. I'm not on any medication except for Evoxac for my dry mouth now"*
- *"I am 12 1/2 years out from radio & chemo therapy. I had Stage 4 SCC on left tonsil which had matastisized to the left TMJ and left base of the tongue. Biotene moisturizing oral rinse is the only product that gives me some relief of dry mouth. 3 month dental hygiene visits, including fluoride varnish treatments, plus prevident 5000 toothpaste which has 2.5 times the amt of fluoride in O-T-C tooth paste. Hyporthyroidism treated with Synthroid 0.075 MCG, once per day"*
- *"Finished with treatment 2 1/2 years; No reoccurrence; continue to have some radiation side effects"*
- *"Radiation IMRT"*
- *"I am 14 years out so I no longer use prescription medication and rely on OTC products"*
- *"I had surgery and radiation"*
- *"Gabapentin 300MG, Lotrel 5/20, Pilocarpine, Zolpidem"*
- *"levothoroxide"*
- *"I am currently done with all treatments and only occasionally take an anti-anxiety. Use products for dry mouth and floride for teeth problems. Have some narrowing in my throat so I have to be careful while drinking and eating"*
- *"During treatment had Cisplatin and radiation treatments"*
- *"Nine years cancer free. Biotene spray and mouthwash is all"*
- *"10 l/2 year survivor of head & Neck, squamous cell carcinoma turmor removed with surgery, Erbitux treatments & radiation"*
- *"I don't know what was used--had about 7 weeks of radiation. Twice had to stop for a week, once because I was burned so badly I lost my voice and really hurt and another time because of the burning inside my throat and mouth"*
- *"I'm a 17-year survivor with residual complaints from treatments"*
- *"Oral sprays and pain killers"*

A total of 26 patients answered the survey question on which therapies were most effective at controlling common aspects of head and neck cancer:

Therapies were most effective at controlling common aspects of head and neck cancer	%
Cisplatin	27.27%
Radiotherapy + cetuximab	11.76%
Paclitaxel	11.76%
Carboplatin	6.67%
Carboplatin + paclitaxel	6.67%
Cisplatin + 5-FU (Fluorouracil)	6.25%
Cetuximab	6.25%

Common side effects of current therapies included: fatigue (66.67%), loss of appetite (59.52%), hair loss (47.62%), and constipation (40.48%). Other reported side effects include: nausea, hypothyroidism, peripheral neuropathy, low blood count, trismus, and infection. CCSN noted that almost half of patient respondents reported that fatigue was the most difficult side effect to

manage, while 18.92% of respondents found that peripheral neuropathy and constipation were the most difficult to manage, followed by nausea and vomiting at 13.51%.

CCSN reported that 76.19% of respondents did not have issues accessing treatment, while 7.14% did have issues accessing treatment. Reasons for access issues included: financial hardship due to cost (11.90%) or supplies or issues with administration (2.38%) and limited availability in my community (2.38%). Of note, some patients indicated more than one issue when attempting to access treatment.

3.1.3 Impact of Squamous Cell Cancer of the Head and Neck and Current Therapy on Caregivers

CCSN included questions in its survey for caregivers relating to challenges caregivers face and how their day-to-day lives have been affected. A total of five caregivers participated in the survey.

Their responses are included below:

- *"He can't eat spicy food at all. This can be challenging in restaurants where they don't always list spices used"*
- *"Finding food that didn't taste bad; or too dry to eat with the lack of saliva and of course the depression and PTSD"*
- *"Food preparation and Insurance companies"*
- *"My husband has been very supportive with everything"*
- *"Preparing meals he can eat; Understanding his continuing tongue discomfort and anxiety"*

3.2 Information about the Drug Being Reviewed

3.2.1 Patient Expectations for and Experiences To Date with Nivolumab

A total of 78% of respondents reported that there are needs in their current therapies that are not being met. These needs include:

- *"Treatment for Radiation Fibrosis Syndrome. Treatment for Xerostomia"*
- *"Can't find any useful or new information for my problems"*
- *"Still can't get my mouth to open up any wider and still trying to learn to chew my food and swallow water and food without choking so frequently"*
- *"Dry mouth"*
- *"Something cheaper than Pilocarpine"*
- *"Very poor communication on possible symptoms, counseling for PTSD"*
- *"Dry Mouth and Swallowing"*

When asked how much of an improvement would be needed from the new drug to make it better than the current treatment, responses included:

- *"Medication that will improve salivation and avoid xerostomia"*
- *"No comment as I handled Cisplatinum without any side effects except fatigue"*
- *"The current cure seems to be radiation, chemo, and surgery so I don't quite understand the question. I guess I would hope for a drug that dissolves the cancer"*
- *"More aggressive prevention/education strategies, especially around HPV 16 and its potentially deadly impact"*
- *"Available to use via Peg Feed"*

Patient respondents indicated that they would like nivolumab to address: reduce side effects from current medications/treatments (68.29%), stop disease progression (43.90%), better able to control symptoms (17.07%), and ease of use (14.63%).

According to CCSN, patients struggling with disease progression and uncertainly about the future are willing to tolerate fairly significant side effects.

None of the respondents have used nivolumab; respondents cited the following reasons below:

- *"I am not familiar with this drug and I have no need for it use at this stage"*
- *"Not available when I went through radio/chemo treatment"*
- *"I was in the clinical trial for Keytruda (Pembrolizumab) and have had complete response (no cancer)"*

3.3 Additional Information

CCSN is a national network of patients, families, survivors, friends, community partners, funders and sponsors who have come together to take action to promote the very best standards of care, whether it be early diagnosis, timely treatment and follow-up care, support for cancer patients, or issues related to survivorship or quality of end of life care.

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 (www.cadth.ca/pcodr). PAG identifies factors that could affect the feasibility of implementing a funding recommendation.

Overall Summary

Input was obtained from all nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. PAG identified the following as factors that could impact the implementation on nivolumab for Squamous Cell Carcinoma of the Head and Neck (SCCHN):

Clinical factors:

- Indication creep into first line setting and other types of head and neck cancers

Economic factors:

- Indefinite treatment duration

Please see below for more details.

4.1 Factors Related to Comparators

PAG identified that there is no standard of care for recurrent or platinum-refractory SCCHN. In most provinces, cetuximab is not funded as palliative treatment of platinum-refractory SCCHN. Single agent chemotherapy such as docetaxel, paclitaxel, methotrexate, gemicitabine, vinorelbine and etoposide is often used after platinum chemotherapy.

4.2 Factors Related to Patient Population

PAG noted that there is a small number of patients with refractory SCCHN.

PAG has concerns of indication creep into first-line setting and recognizes that nivolumab in first-line treatment of SCCHN is out of scope of this review. PAG also has concerns that first-line platinum based chemotherapy would be stopped earlier in favour of switching patients to nivolumab earlier and is seeking guidance on the definition of platinum-refractory and recurrence. PAG is also seeking information and guidance on the use of nivolumab in patients who cannot receive platinum based chemotherapy and would be treated with cetuximab in the first-line.

PAG is seeking information on whether it is appropriate to extrapolate the results of the submitted trial to the following patients who have failed first-line platinum chemotherapy:

- Naso-pharyngeal, tongue, or salivary gland cancers
- Non-squamous head and neck cancer
- HPV positive head and neck cancer

PAG is seeking guidance on whether it would be appropriate to switch to nivolumab for patients who are currently undergoing a second-line chemotherapy treatment but not yet progressed. PAG is also seeking guidance on the appropriateness of providing patients who have received second-line treatment and have progressed with the opportunity to receive nivolumab. PAG is also seeking information on the treatments after failure of nivolumab, recognizing this may be out of scope of this review.

4.3 Factors Related to Dosing

The funding request is for a dose of 3mg/kg every two weeks. PAG is seeking information on whether a fixed dose of 240mg for SCCHN patients would be appropriate.

PAG is seeking guidance on treatment duration and discontinuation criteria

4.4 Factors Related to Implementation Costs

PAG noted that there would be drug wastage given the small number of patients and the weight based dose. However, PAG also noted that vial sharing is possible in larger centres as nivolumab could be used for other indications. However, if the flat dose of nivolumab can be used in all indications, there would be no wastage.

As treatment is until progression or unacceptable toxicity, the indefinite or unknown treatment duration may be a barrier to implementation

4.5 Factors Related to Health System

PAG noted that more resources and chemotherapy chair time would be required to monitor for infusion reactions and adverse effects of nivolumab compared to standard chemotherapy.

4.6 Factors Related to Manufacturer

None identified.

5 SUMMARY OF REGISTERED CLINICIAN INPUT

Registered clinician input was not received for this review

6 SYSTEMATIC REVIEW

6.1 Objectives

To evaluate the efficacy and safety of nivolumab as a monotherapy in patients with recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN) after receiving platinum-based therapy.

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 the table below. 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 3: Selection Criteria

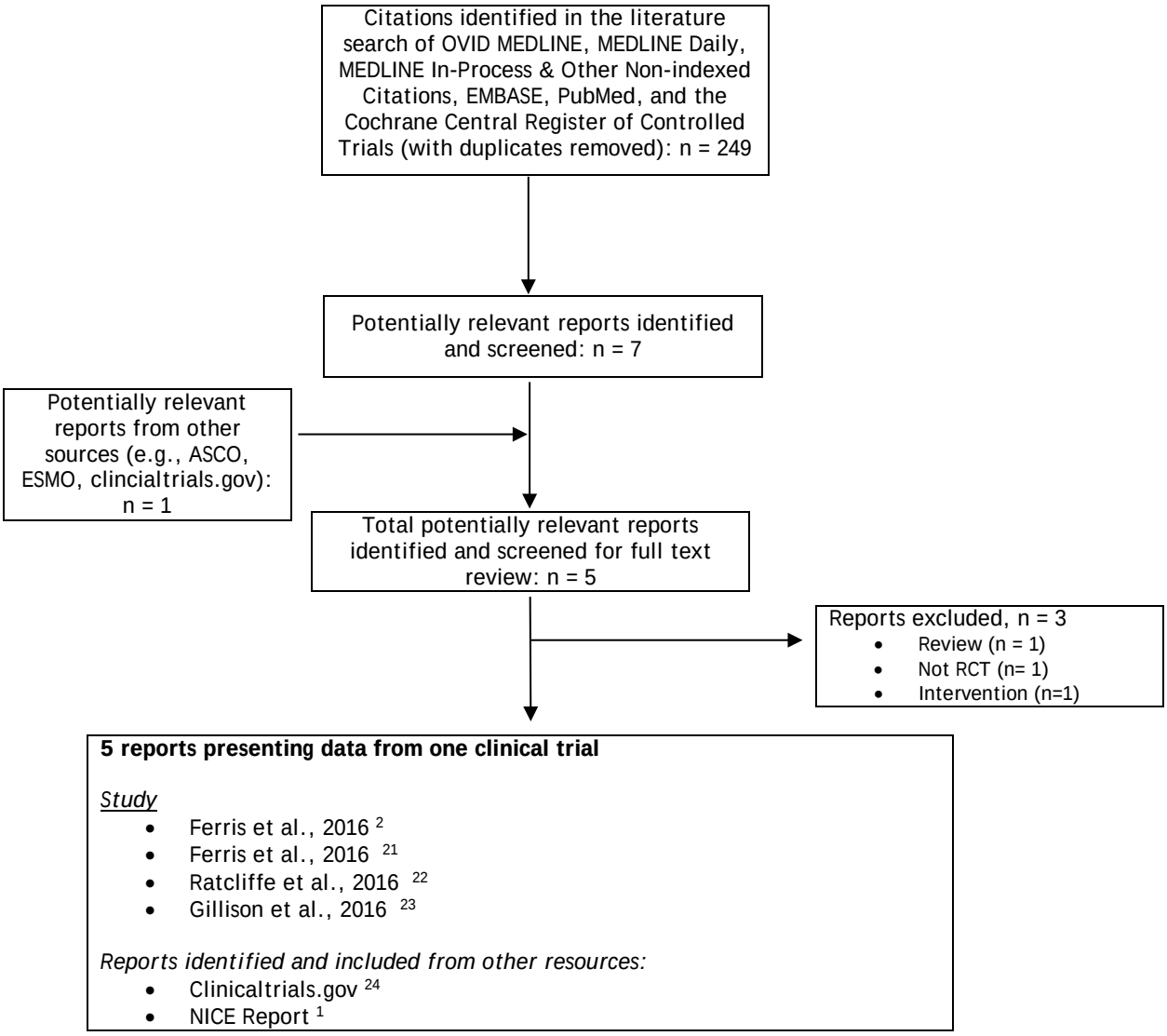
Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
Published or unpublished RCTs In the absence of RCT data, fully published clinical trials investigating the safety and efficacy of nivolumab should be included.	Patients with recurrent or metastatic SCCHN after platinum-based therapy Subgroups: • Intended standard therapy (cetuximab vs other agents) • PD-L1 expression (1%, 5% or 10%) • HPV-16 status (positive vs negative)	Nivolumab	Single agents • Docetaxel • Paclitaxel • Methotrexate • Gemcitabine • Vinorelbine • Etoposide Best supportive care	Primary • OS • PFS • PRO Secondary • ORR • DOR • DCR Safety • AEs • SAEs • WDAEs • Autoimmune AEs
RCT=randomized controlled trial; SCCHN = squamous cell carcinoma of the head and neck; PD-L1 = Programmed death-ligand 1; HPV-16 = Human papillomavirus type 16; PRO=Patient related outcomes; AE=adverse events; SAE=serious adverse events; WDAE=withdrawals due to adverse events; DCR=disease control rate; ORR=objective response rate; DOR=duration of response				
Notes: * 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 249 potentially relevant reports identified, one study (Checkmate 141) reported in five citations was included in the pCODR systematic review.[2,21-24] Three studies were excluded because one was not a randomized controlled (RCT) trial [25], one was a review [26] and one trial did not have a relevant therapeutic agent therapy [27,28].

Figure 1. PRISMA Flow Diagram for Inclusion and Exclusion of studies



Note: Additional reports related to Checkmate 141 were obtained from the Submitter [Module 2.5[5], Module 2.7.3[29] Clinical Summary Report[30]]

6.3.2 Summary of Included Studies

The pCODR systematic review identified one open-label, phase III RCT (Checkmate 141). This trial assessed the efficacy and safety of nivolumab as compared standard therapy in 361 patients with recurrent squamous-cell carcinoma of the head and neck (SCCHN) whose disease had progressed within 6 months after platinum-based chemotherapy.[2] The summary of the trial and select quality characteristics are presented in Table 4 and Table 5.

Table 4: Summary of Trial Characteristics of the Included Studies

Trial Design	Eligibility Criteria	Intervention and Comparators	Trial Outcomes
Checkmate 141 **Other identifiers:** NCT02105636 **Characteristics:** Phase III, open-label, RCT **Sample size:** Randomized: 361 **Locations:** 55 sites in 15 countries (Argentina, Brazil, Canada, France, Germany, Hong Kong, Italy, Japan, Korea, Netherlands, Spain, Switzerland, Taiwan, the UK, and the US) **Patient Enrolment Dates:** 06/2014 to 08/2015 **Primary Analysis Data cut-off:** 18-Dec-2015 **Estimated Study Completion Date:** 09/2018 **Sponsor:** Bristol-Myers Squibb	<u>Key Inclusion Criteria:</u> • Adults aged 18 years or older with an ECOG of 0 or 1 • Histologically confirmed, recurrent or metastatic SCCHN of the oral cavity, pharynx, or larynx that was not amenable to curative treatment • Tumour progression or recurrence within 6 months after the last dose of platinum-containing chemotherapy administered as adjuvant therapy or in the context of primary or recurrent disease • Adequate bone marrow, hepatic, and renal function • Measurable disease according to RECIST version 1.1 <u>Key Exclusion Criteria:</u> • Active brain metastases, autoimmune disease or systemic immunosuppression • Known HIV or hepatitis B or C virus infection • Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CTLA-4 antibody	**Intervention:** Nivolumab at 3mg/kg every 2 weeks **Comparator:** Cetuximab at 400 mg/m^2 once followed by 250 mg/m^2 weekly OR Methotrexate at 40-60 mg/m^2 weekly OR Docetaxel at 30-40 mg/m^2 weekly	<u>**Primary:**</u> OS <u>**Secondary:**</u> PFS ORR <u>**Exploratory:**</u> DOR TTR Safety and tolerability PROs PK parameters
RCT = Randomized controlled trial; **SCCHN** = squamous cell carcinoma of the head and neck; **ECOG** =Eastern Cooperative Oncology Group Performance Status; **RECIST** = Response Evaluation Criteria In Solid Tumours; **PFS** = Progression-free survival; **OS** = Overall Survival; **ORR** = Overall response rate; **DOR** = Duration of response; **TTR** = Time to response; **PRO** = Patient reported outcome; **PK** = pharmacokinetics.			

Table 5: Select quality characteristics of included studies of nivolumab in patients with recurrent or metastatic SCCHN who have received platinum-based therapy

Study	Treatment vs. Comparator	Primary outcome	Required sample size [A]	Sample size	Randomization method [B]	Allocation concealment	Blinding [C]	ITT Analysis	Final analysis [D]	Early termination	Ethics Approval
CheckMate 141	Nivolumab vs. standard therapy	OS	360 (based on 278 deaths)	361	IVRS, stratified	Yes	No	Yes	No	Yes	Yes

Abbreviations: ITT = intention to treat; IVRS = interactive voice response service; OS = overall survival

A: 360 patients were required to provide 90% power to reject the null hypothesis of an HR of 0.667 (278 deaths) using a two-sided significance level of α=0.05. The power calculation also allowed for one interim analysis.
B: Randomization was stratified by previous cetuximab (yes/no).
C: Investigators and patients were not blinded to treatment assignment. In fact, chemotherapy treatment was guided by the study investigator. PFS and all other secondary outcomes were confirmed by investigator assessment.
D: The interim overall survival data was reviewed by a Data Monitoring Committee on 26-Jan-2016. The trial was stopped early based on the DMC assessment that the study met its primary endpoint with nivolumab demonstrating superiority to standard therapy on overall survival. The interim database lock occurred on 18-Dec-2015 and the study is still ongoing.[5]

6.3.2.1 Detailed Trial Characteristics

a) Trials

One phase III, RCT met the inclusion criteria of the pCODR systematic review, Checkmate 141 (N = 361) (Table 4, Table 5 and Figure 1).

Checkmate 141 was a multicenter, open-label phase III RCT that assessed the safety and efficacy of nivolumab as compared to standard therapy in patients with recurrent or metastatic SCCHN.[2] The trial was conducted in 55 sites in 15 countries, which includes: Argentina, Brazil, Canada, France, Germany, Hong Kong, Italy, Japan, Korea, Netherlands, Spain, Switzerland, Taiwan, the UK, and the US.[30] The trial was funded by Bristol-Myers Squibb Canada.

Patient enrolment occurred between June 2014 and August 2015.[2] The trial included patients aged 18 years and older who had an ECOG status of 0 or 1 and histologically confirmed recurrent or metastatic SCCHN of the oral cavity, pharynx, or larynx that was not amenable to curative treatment. Patients also had to have tumour progression or recurrence that occurred within 6 months after their last dose of platinum-containing chemotherapy. This chemotherapy had to be administered as an adjuvant therapy or in the context of primary or recurrent disease. Patients were also eligible if they had adequate bone marrow, hepatic, and renal function and measureable disease according to Response Evaluation Criteria in Solid Tumours (RECIST) 1.1.[2] Patients were ineligible if they had active brain metastases, autoimmune disease or systemic immunosuppression, prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CTLA-4 antibody or known HIV, hepatitis B or hepatitis C virus infection.

Eligible patients were randomized (2:1) to receive treatment with nivolumab (N = 240) or standard therapy, which consisted of a single-agent therapy of the investigator's choice (N = 121). In this arm, patients were treated with methotrexate (40-60 mg/m^2; N = 52), docetaxel (30-40 mg/m^2; N = 54) or cetuximab (400 mg/m^2 followed by 250 mg/m^2; N = 15).[2] Randomization was stratified by previous cetuximab therapy and the authors used an intention-to-treat (ITT) analysis.

There were three phases in this trial, which include treatment, follow-up and the nivolumab extension arm.[3] The following phases will be described in more detail:

Treatment Phase

- Patients were randomly assigned (2:1) to either the nivolumab treatment group or the standard therapy treatment group using an interactive voice response system (IVRS)
- Randomization was stratified by prior cetuximab treatment
- Patients are evaluated for response using the RECIST 1.1 criteria and tumour assessments occurred at Week 9 and then every 6 weeks
- Patients were treated until they had disease progression or they discontinue from their assigned therapy

Follow-up Phase

- Treatment beyond initial investigator-assessed progression was allowed for patients randomized to the nivolumab arm if they demonstrated investigator-assessed clinical benefit and they were tolerant to the study drug
- Patients were followed up for safety within 100 days from the last dose of study therapy
- Patients were followed for overall survival every 3 months until death, lost to follow-up or withdrawal of study consent
- Patients who discontinued treatment for reasons other than disease progression were monitored until disease progression, lost to follow-up or withdrawal of study consent

Nivolumab Extension Phase

- Treatment beyond initial investigator-assessed progression was allowed for patients randomized to the nivolumab arm if they demonstrated investigator-assessed clinical benefit and they were tolerant to the study drug
    - Patients could continue to receive nivolumab beyond initial RECIST progression if they met the following criteria[3]:
        - Investigator assessed clinical benefit and do not have rapid disease progression;
        - Tolerance of study drug;
        - Stable performance status;
        - Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (e.g. CNS metastases);
        - Subject provides written informed consent prior to receiving any additional nivolumab treatment, using an ICF describing any reasonably foreseeable risks or discomforts, or other alternative treatment options.
- A protocol amendment (11-Feb-2016) allowed eligible patients who were randomized to the standard therapy arm to be treated with nivolumab until progression or unacceptable tolerability. The rationale for this amendment was based on a recommendation made by the independent Data Monitoring Committee (DMC) of Checkmate 141. On 26-Jan-2016, the DMC evaluated the interim analysis of overall survival and declared that nivolumab was superior to standard therapy. Based on this decision, the protocol was amended so that eligible patients assigned to standard therapy could receive subsequent nivolumab therapy in the Nivolumab Extension Phase.[3]

The primary outcome assessed in the Checkmate 141 Trial was overall survival. The trial was designed to have 90% power to reject the null hypothesis of a hazard ratio (HR) of 0.667 (278 deaths) using a two-sided significance level of α=0.05 .[2] The design of the trial also enabled the study investigators to conduct one interim analysis using stopping boundaries based on an O'Brien–Fleming alpha-spending function.[2] The key secondary outcomes in CheckMate 141 were progression free survival (PFS) and objective response rate (ORR) according to RECIST 1.1.

Exploratory outcomes included: duration of response (DOR); time to response (TTR); safety and tolerability; patient related outcomes (PRO); pharmacokinetic (PK) parameters.

The Manufacturer reported that three database locks were used for this trial. The first database lock was on 18-December-2015 (interim analysis of overall survival and safety events), the second was on 03-Feb-2016 (PD-L1 analysis) and the final database lock was on 05-May-2016 (ORR and PFS analysis).[5]

The study protocol was amended 11 times. The abbreviated protocol amendments included: administrative changes and clarifications to procedures, concomitant treatments, and eligibility criteria; changes to the primary endpoints from PFS and overall survival (co-primaries) to overall survival alone and to increase the sample size to target a hazard ratio for overall survival that was in line with external data; to change the trigger for the interim analysis of overall survival; and to allow patients who were originally assigned to standard therapy arm to enter the nivolumab extension phase.[31]

In total, 11.9% of patients had at least one protocol deviation, where 13.3% of deviations occurred in the nivolumab arm and 9.1% occurred in the standard therapy arm.[31] At the entrance of the study, the most common reason for a protocol deviation in both treatment groups was progression associated with last prior platinum regimen > 6 months after the last dose of platinum (nivolumab: 7.5% and standard therapy: 3.3%). On the other hand, on-treatment deviations were most likely to occur because patients received a concurrent anti-cancer therapy in both the nivolumab (3.8%) and standard therapy arms (1.7%).[31]

b) Populations

The study baseline characteristics are presented in Table 6. It was noted that patient characteristics were generally balanced between the nivolumab and standard therapy groups with the exception of smoking history (P = 0.047).[2] However, there was a ≥ 5% difference between the treatment groups for several baseline characteristics, which include: tobacco use (never smokers [nivolumab: 16.2% vs. standard therapy: 25.6%]), context of previous systemic therapy regimen (neoadjuvant therapy [nivolumab: 7.1% vs. standard therapy: 13.2%]), site of primary tumour (oral cavity [nivolumab: 45.0% vs. standard therapy: 55.4%]) and number of previous lines of systemic cancer therapy (≥ 3 [nivolumab: 22.5% vs. standard therapy: 14.9%]).[2]

Overall, the median age of patients in the trial was 60 years of age (range: 28 to 83). The majority of these patients were male (83.1%), Caucasian (83.1%), current or former smokers (76.5%), had an ECOG performance status of 1 (78.4%), received one line of previous therapy (45.4%), had a primary tumour in their oral cavity (48.5%) and had previously been treated with cetuximab (61.5%) (Table 6).

Table 6: Baseline Patient Characteristics for CheckMate 141

Characteristic	Nivolumab (N = 240)	Standard Therapy (N=121)	Total (N = 361)
Median Age, (range) ≥75 years, n (%)	59 (29-83) 12 (5.0)	61 (28-78) 6 (5.0)	60 (28-83) 18 (5.0)
Sex Men, n (%)	 197 (82.1)	 103 (85.1)	 300 (83.1)

Characteristic	Nivolumab (N = 240)	Standard Therapy (N=121)	Total (N = 361)
Race[A], n (%)			
White	196 (81.7)	104 (86.0)	300 (83.1)
Asian	29 (12.1)	14 (11.6)	43 (11.9)
Black	10 (4.2)	3 (2.5)	13 (3.6)
Other	5 (2.1)	0	5 (1.4)
ECOG Performance Status, n (%)			
0	49 (20.4)	23 (19.0)	72 (19.9)
1	189 (78.8)	94 (77.7)	283 (78.4)
≥2	1 (0.4)	3 (2.5)	4 (1.1)
Not Reported	1 (0.4)	1 (0.8)	2 (0.6)
Smoking Status, n (%)			
Current or Former Smoker	191 (79.6)	85 (70.2)	276 (76.5)
Never Smoker	39 (16.2)	31 (25.6)	70 (19.4)
Not Reported	10 (4.2)	5 (4.1)	15 (4.2)
Context of previous systemic therapy regimen[B], n (%)			
Primary Disease	173 (72.1)	83 (68.6)	256 (70.9)
Metastatic Disease	112 (46.7)	59 (48.8)	171 (47.4)
Adjuvant Therapy	37 (15.4)	21 (17.4)	58 (16.1)
Neoadjuvant Therapy	17 (7.1)	16 (13.2)	33 (9.1)
Previous Lines of Therapy[C], n (%)			
1	106 (44.2)	58 (47.9)	164 (45.4)
2	80 (33.3)	45 (37.2)	125 (34.6)
≥3	54 (22.5)	18 (14.9)	72 (19.9)
Site of Primary Tumour, n (%)			
Larynx	34 (14.2)	15 (12.4)	49 (13.6)
Oral Cavity	108 (45.0)	67 (55.4)	175 (48.5)
Pharynx	92 (38.3)	36 (29.8)	128 (35.5)
Other[D]	6 (2.5)	3 (2.5)	9 (2.5)
Tumour PD-L1 Expression Level, n(%)			
PD-L1 ≥ 1%	88 (36.7)	61 (50.4)	149(41.3)
PD-L1 < 1%	73 (30.4)	38 (31.4)	111(30.7)
PD-L1 ≥ 5%	54 (22.5)	43 (35.5)	97(26.9)
PD-L1 < 5%	107 (44.6)	56 (46.3)	163(45.2)
PD-L1 ≥ 10%	43 (17.9)	34 (28.1)	77(21.3)
PD-L1 < 10%	118 (49.2)	65 (53.7)	183(50.7)
Not quantifiable	79 (32.9)	22 (18.2)	101(28.0)
p16 Status, n (%)			
Positive	63 (26.2)	29 (24.0)	92 (25.5)
Negative	50 (20.8)	36 (29.8)	86 (23.8)
Previous receipt of cetuximab, n (%)	150 (62.5)	72 (59.5)	222 (61.5)

A: Race was self-reported
B: Patients may have received previous systemic therapy in more than one context.
C: A line of systemic chemotherapy was defined as any chemotherapy that was administered as part of primary therapy for squamous-cell carcinoma of the head and neck (e.g., induction or concurrent chemoradiotherapy) or any single-agent or multiple-agent chemotherapy regimen that was administered after a diagnosis of recurrent squamous-cell carcinoma of the head and neck.
D: The "Other" category included patients with a tumor in more than one of the categories (i.e., larynx, oral cavity, or pharynx).
Source: Ferris et al, (2016). NEJM.[2]

All patients enrolled in the Checkmate 141 Trial had received prior platinum therapy in the adjuvant, primary, recurrent or metastatic setting.[5] The Manufacturer reported that 40.4% of patients progressed on their most recent platinum-based regimen. In addition, 93.9% progressed on or within 6 months to a prior therapy while almost half of all patients progressed within two months.[29] The Manufacturer also noted that 3.6% of patients (N =13) had progressed more than 6 months after their most recent platinum-based regimen and all of these patients were considered as protocol deviations.[29]

The majority of all patients (61.5%) received cetuximab as a prior treatment and over half of these patients (54.6%) had more than one line of pervious therapy.[2]The Manufacturer stated that prior systemic therapies were balanced across groups and the most frequently reported therapies were cisplatin (nivolumab: 74.6% and standard therapy: 75.2%); cetuximab (nivolumab: 62.5% and standard therapy: 59.5%); carboplatin (nivolumab: 54.2% and standard therapy: 54.5%); fluorouracil (nivolumab: 50.0% and standard therapy: 50.4%); docetaxel (nivolumab: 33.8% and standard therapy: 35.5%), and paclitaxel (nivolumab: 27.9% and standard therapy: 22.3%).[29]

c) Interventions

Patients in the Checkmate 141 trial were randomized to receive either nivolumab (N = 240) or standard therapy (N = 121). The single agent systemic therapies used in the standard arm were methotrexate, docetaxel and cetuximub. The Manufacturer stated that these agents were selected because they are active in the platinum refractory setting and they have regulatory approval for use in this indication.[30] Methotrexate and docetaxel have been approved in Canada for the treatment of SCCHN while cetuximub has not been approved or available in Canada for this indication. In the protocol, it was stated that patients in the standard therapy arm can only be assigned a single agent if they have not already received it for prior therapy of metastatic SCCHN.[3]

Patients in Checkmate 141 were treated with one of the following regimens:

- Nivolumab: 3 mg/kg intravenous (IV) dose of nivolumab every two weeks.
- Cetuximab: 400 mg/m^2 IV dose of cetuximab followed by 250 mg/m^2 weekly
- Methotrexate: 40-60 mg/m^2 IV dose of methotrexate weekly
- Docetaxel: 30-40 mg/m^2 IV dose of docetaxel weekly

Dose reductions were not permitted for the nivolumab treatment group; however, patients were allowed to be treated beyond progression (either clinical or radiological) if they met the following criteria[3]:

- Investigator-assessed clinical benefit and do not have rapid disease progression
- Tolerance of the study drug
- Stable performance status
- Treatment beyond progression will not delay an intervention that might prevent a serious complication of disease progression

Dose reductions were only permitted in the standard therapy arm (Table 7). It was reported that 25.2% of patients in the standard therapy arm experienced at least one dose reduction which resulted from an adverse event (70.6%).[2]

Dose delays were permitted regardless of the patient's randomization status. A patient could return to their assigned therapy once the treatment-related AE was resolved to baseline or Grade ≤ 1.[3] Half of the patients in the standard therapy arm (50.4%) and 32.6% of patients in the nivolumab arm experienced at least one dose delay.[2] The most common reason for a dose delay,

in both treatment arms, was due to an adverse event (nivolumab: 53.3% and standard therapy: 63.6%).

Table 7. Dose modification, delay or discontinuation in CheckMate 141

	Nivolumab	Standard Therapy
Patients with at least 1 dose delay, n (%)	77 (32.6)	56 (50.4)
Reasons for dose delay		
Adverse event	64 (53.3)	77 (63.6)
Other	56 (46.7)	36 (29.8)
Not reported	0	8 (6.6)
Patients with at least 1 dose reduction, n (%)	NA	28 (25.2)
Reasons for dose reduction		
Adverse event		24 (70.6)
Protocol defined		3 (8.8)
Other		1 (2.9)
Not reported		5 (14.7)
Source: Ferris et al, (2016). NEJM.[2,4]		

d) Patient Disposition

The patient disposition is presented in Table 8. In total, 506 patients were eligible for enrollment in the trial, and 361 were randomized to receive nivolumab (N = 240) or standard therapy (N = 121; methotrexate, N = 52; docetaxel, N = 54; and cetuximab, N = 15).[2,4] In the nivolumab arm, 1.7% of patients did not receive treatment because of disease progression (0.4%), they requested to discontinue treatment (0.4%) or they no longer met the study criteria (0.8%).[29] However, in the standard therapy arm, 8.3% of patients did not receive their intended therapy because they requested to discontinue treatment (1.7%), they withdrew consent (5%) or they no longer met the study criteria (1.7%).[4]

The median duration of therapy for both the nivolumab arm and the standard therapy arm was 1.9 months.[29] Among those in the standard therapy arm, the median duration of therapy was longer in patients treated with docetaxel (2 months) as compared to those treated with methotrexate or cetuximab (1.6 months).[29]

More patients in the standard therapy arm (97.3%) discontinued treatment compared to those on the nivolumab arm (82.6%).[2] The primary reason for discontinuation was due to disease progression (68.6% in nivolumab group and 74.8% in the standard therapy group); however, more patients in the standard therapy group discontinued treatment due to study toxicity as compared to those in the nivolumab group (9.9% vs. 3.8%, respectively).[29] At the time of the interim analysis, 17.4% of the patients in the nivolumab group and 2.7% in the standard therapy group were still receiving treatment.[2]

Table 8: Patient disposition for the Checkmate 141 Trial

	Nivolumab N = 240	Standard Therapy N = 121	Total N = 361
Patients randomized[A]			
Not treated	4 (1.7)	10 (8.3)	14 (3.9)
Primary reason for not being treated			
Disease progression	1 (0.4)	0	1 (0.3)
Subject request to discontinue study	1 (0.4)	2 (1.7)	3 (0.8)

	Nivolumab N = 240	Standard Therapy N = 121	Total N = 361
treatment			
Subject withdrew consent	0	6 (5.0)	6 (1.7)
Subject no longer meets study criteria	2 (0.8)	2 (1.7)	4 (1.1)
Subjects treated	236	111	347
Subjects continuing in the treatment period	41 (17.4)	3 (2.7)	44 (12.7)
Subjects not continuing in the treatment period	195 (82.6)	108 (97.3)	303 (87.3)
Reason for not continuing in the treatment period			
Disease progression	162 (68.6)	83 (74.8)	245 (70.6)
Study drug toxicity	9 (3.8)	11 (9.9)	20 (5.8)
Adverse event unrelated to study drug	12 (5.1)	3 (2.7)	15 (4.3)
Subject request to discontinue study treatment	4 (1.7)	6 (5.4)	10 (2.9)
Subject withdrew consent	4 (1.7)	1 (0.9)	5 (1.4)
Maximum clinical benefit	1 (0.4)	1 (0.9)	2 (0.6)
Poor/non-compliance	0	1 (0.9)	1 (0.3)
Other	0	2 (1.8)	2 (0.6)
Not reported	3 (1.3)	0	3 (0.9)

A: Patients ongoing at the time of the cut-off 18-Dec-2015 database lock
Source: Module 2.7.3[29]

At the 05-May-2016 database lock, 35.0% of patients on the nivolumab arm and 38.0% of patients on the standard therapy arm received subsequent cancer therapy (Table 9).[29] Here, 29.6% and 32.2% of patients in the nivolumab and standard therapy groups were treated with a systemic therapy.[29] Among those randomized to the nivolumab group, 1.3% received a subsequent anti-PD-1 therapy (nivolumab, n = 2; pembrolizumab, n =1) as compared to 7.4% patients randomized to the standard therapy arm (nivolumab, n = 1; pembrolizumab, n = 8).[30]

Table 9: Subsequent therapies patients received after discontinuing from nivolumab or standard therapy (investigator's choice)[30]

Subsequent agent	Number of patients (%)	
	Nivolumab arm N=240	Investigator's choice arm N=121
Subjects with any subsequent therapy	84 (35.0)	46 (38.0%)
Subsequent radiotherapy	29 (12.1)	12 (9.9)
Subsequent surgery	1 (0.4)	2 (1.7)
Subsequent systemic therapy	71 (29.6)	39 (32.2)
Methotrexate	17 (7.1)	7 (5.8)
Carboplatin	9 (3.8)	6 (5.0)
Cetuximab	23 (9.6)	10 (8.3)
Docetaxel	10 (4.2)	4 (3.3)
Paclitaxel	6 (5.0)	19 (7.9)

As previously mentioned, patients in the nivolumab and standard therapy group had the option of being treated beyond progression, which was defined as the last dosing date after RECIST 1.1

progression.[30] There were 24.6% (n=58/236) of patients in the nivolumab group who were treated beyond progression.[30] However, a protocol amendment (11-Feb-2016) was made by the independent DMC to allow patients originally assigned to the standard therapy to receive subsequent nivolumab therapy in the Nivolumab Extension Phase because nivolumab was superior to standard therapy at the interim analysis.[3] Thus none of the patients initially assigned to the standard therapy treatment group received nivolumab beyond disease progression.

e) Limitations/Sources of Bias

Checkmate 141 was a multicentre, open-labeled phase III, randomized controlled trial. Overall, the trial was well designed; however, there are a few limitations that need to be considered:

- Checkmate 141 was an open-label RCT design. A double-blinded design would have been very difficult to implement due to the assignment of chemotherapy agents (i.e. cetuximab, methotrexate or docetaxel). The assessment of overall survival will not be influenced by the open-label nature of the trial because it is an objective outcome.[32,33] Yet, for the assessment of subjective outcomes, such as PRO and adverse events, there is a greater risk of detection bias because patients and study investigators are aware of which treatment was being administered.

- In the standard therapy arm, patients were randomized to methotrexate (43%), docetaxel (45%) and cetuximab (12.4%).[2] Although methotrexate and docetaxel have been approved for the treatment of SCCHN in Canada, cetuximub has not been approved or available in Canada. In addition, a subgroup analysis demonstrated a greater benefit of nivolumab as compared to cetuximab (HR: 0.47, 95% CI: 0.22–1.01), which may bias the results in favour of nivolumab.[2] However, only 15 patients were treated with cetuximab in the trial, and since the effect estimates were similar to docetaxel and methotrexate, the impact was considered minimal.

- Among all of the randomized patients, 10 patients (8.3%) did not receive standard therapy and four (1.7%) did not receive nivolumab.[2] Reasons for exclusion were patient requested to discontinue treatment (n =3), patient withdrew consent (n = 6), disease progression (n=1) and patient no longer met study criteria (n=4). To address the exclusion of these patients the Manufacturer performed a per protocol analysis on overall survival and PFS (data not shown due to disclosure reasons).[31] The results of this re-analysis showed that the unbalanced exclusion did not impact the reported effect estimates because similar overall survival and PFS were observed.

- There was a ≥ 5% difference between the treatment groups for several baseline characteristics, such as: tobacco use, context of previous systemic therapy regimen, site of primary tumour and number of previous lines of systemic cancer therapy.[2] These factors represent potential confounders and they may bias effect estimates in either direction. Upon request, the Manufacturer provided the p-value for interaction for the association between treatment group and overall survival stratified by tobacco use, context of previous systemic therapy regimen, site of primary tumour and number of previous lines of systemic cancer therapy. The p-value for interaction was not significant for any of the factors (p-value for interaction > 0.05 for all).[31]

- Data for PROs were collected at week 9 (± 1 week) and every 6 weeks (± 1 week) thereafter. It is unclear why intervals of 6 weeks were chosen to collect patient reported outcomes. Based on the available evidence, by the second data collection period for PRO's (week 15), the majority of patients in the standard therapy group had progressed and were no longer available (n=30/121) patients remaining on study). Therefore uncertainty

remains in the interpretation of patient report outcomes in the standard therapy group as the time intervals used to collect data may not have captured the true quality of life impact of standard therapy on patient's quality of life. Although more patients were available for data collection in the nivolumab group, limitations related to the chosen time interval for data collection also apply in the nivolumab group.

- The Manufacturer reported that the effect of immunotherapies may not be adequately represented by antitumor activity measures since tumour response differs for these therapies as compared to chemotherapy. This phenomenon, pseudo-progression, occurs in patients treated with immunotherapies, is characterised by radiologic disease growth which may be due to immune-related inflammation and not necessarily reflective of true disease progression. For instance, these patients may experience an initial increase in tumour size prior to it shrinking. This change in tumour size has the potential to be misinterpreted as disease progression (as defined by iRECIST guidelines).

- The median overall survival may underestimate the potential long-term effect of these therapeutic agents since the Kaplain-Meier plots are characterized by plateaus and long tails.[30] Additionally, the mean overall survival may be underestimated because the mean overall survival can be greatly affected by outliers with extremely short survival.[30]

- In order to control for type I error, the authours implemented a hierarchical testing approach if the effect estimate of overall survival was significant.[3] The key secondary endpoints were tested in the following hierarchical order: 1) PFS as per investigator among randomized patients, and 2) ORR as per investigator among all randomized patients. However, the reported effect estimate of PFS was not significant and it is uncertain if the ORR estimates were adequately controlled for multiplicity.

- Although there was a significant treatment effect for overall survival, the Kaplan-Meier plots for the two treatment arms cross each other (e.g. Figures 2) around months 2 and 3.[2] This may increase the uncertainty in the effect estimates as it suggests the hazard for death is not constant over time, which is an assumption required for the Cox proportional hazards model. One option for addressing this issue is by stratifying the estimated hazard ratio. Here, Cox regression models are fit at different time frames to obtain different hazard ratios. However, these methods reduce the sample size, and increase the likelihood of type 2 error. In response to a pCODR request, the Manufacturer provided a Wald test and a plot examining the evolution of the overall survival HR over time. Given this evidence, it is difficult to interpret the hazard ratio in the trial as an "average" of the curves over time (or the average of the different hazard ratios after stratifying by different time frames). Qualitatively, the overall analyses favour nivolumab over standard therapy, but there is uncertainty associated with the actual effect size.

6.3.2.2 Detailed Outcome Data and Summary of Outcomes

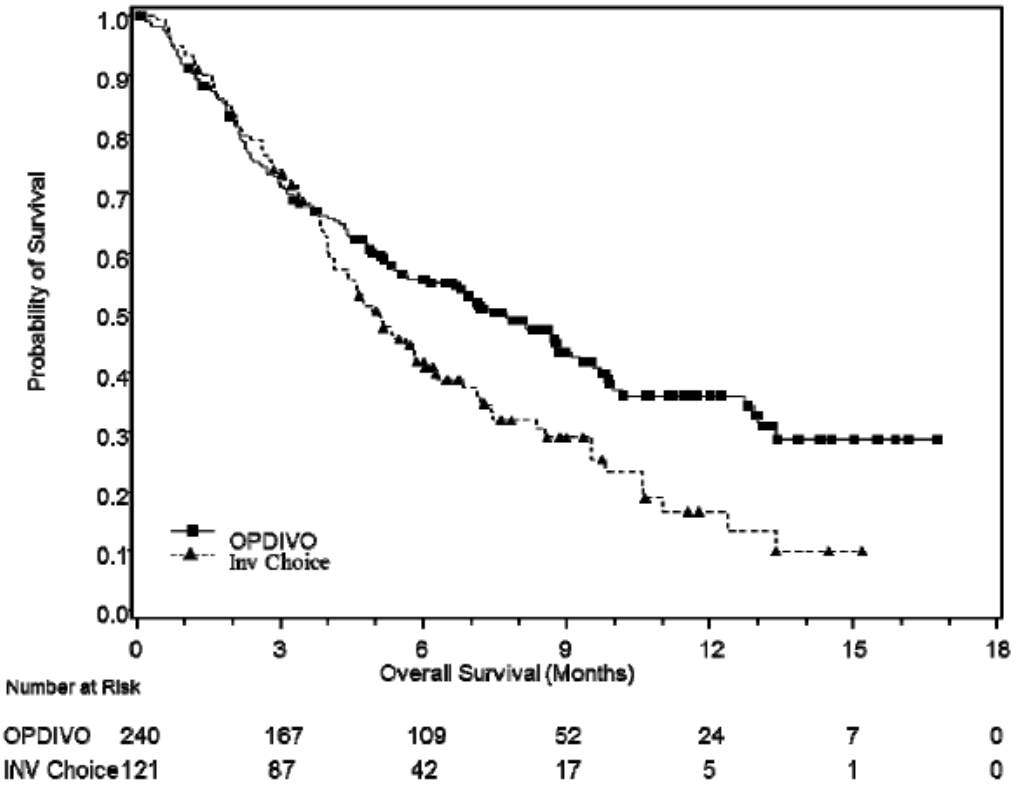
Efficacy Outcomes

Overall survival

Overall survival was the primary outcome in Checkmate 141 and it was defined as the time from randomization to the date of death from any cause.[24] Patients were censored at the date they were last known alive, or if patients did not have follow-up, they were censored at the date of randomization.[24] Median overall survival was assessed using Kaplan-Meier plots and effect estimates were obtained using Cox proportional hazard ratios (HR) and with corresponding confidence intervals (CI).[24]

The protocol stated that 278 deaths were required to occur to have 90% power for a two-sided α=0.05 level with an expected HR of 0.667.[3] An interim analysis was also planned after 195 (70%) deaths had occurred or 6 months after the last subject was randomized, whichever occurred first.[3] For the interim analysis, stopping boundaries were based on the number of overall survival events using the Lan-DeMets alpha spending function with O'Brien-Fleming boundaries, controlling for an experiment wise two-sided alpha of 5%.[3] To account for the interim analysis, a CI of 97.73% was used for the overall survival HR.

Figure 2: Kaplan-Meier plot of overall survival stratified by treatment group



Source: FDA Nivolumab Label[34]

The planned interim analysis was conducted on 18-Dec-2015, which represents 5.1 months (range 0 to 16.8) of follow-up.[2] Figure 2 represents the Kaplan-Meier curves of overall survival. At the database lock, 55.4% of patients in the nivolumab group (N = 133) and 70.2% of patients in the standard therapy group died (N = 85).[2] The median overall survival in the nivolumab group was 7.5 months (95% CI: 5.5 to 9.1) and 5.1 months (95% CI: 4.0 to 6.0) in the standard therapy group.[2] SCCHN patients treated with nivolumab had a 30% reduction in the risk of death as compared those treated with standard therapy; HR of 0.70, 97.73% CI, 0.51 to 0.96; P = 0.01).[2]

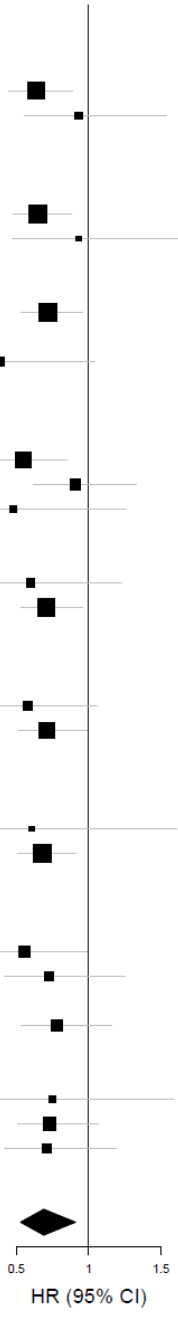
Ferris et al (2016) commented that the delayed separation in the Kaplan-Meier curves was due to nonproportionality.[2] The authours highlighted that the overall survival rate was higher in the nivolumab group as compared to the standard therapy group at 6 months [55.6% (95% CI: 48.9 to 61.8) vs. 41.8% (95% CI: 32.6 to 50.7)] and at 12 months [36.0% (95% CI: 28.5 to 43.4) vs. 16.6% (95% CI: 8.6 to 26.8)].[24]

Pre-specified subgroup analyses were also performed for overall survival. For the purpose of this review, the subgroups were divided in two categories, 1) baseline characteristics (i.e. age, gender, race, region, ECOG status, tobacco use, disease at entry, HPV-16 status and site of primary tumour) and 2) prior treatments (i.e. prior cetuximab use, intended investigator's choice, prior surgery and/or radiotherapy, best response to the most recent regimen, time from initial diagnosis to randomization and prior lines of systemic therapy and/or chemotherapy).

The baseline characteristic subgroup analysis for overall survival is presented in Figure 3. There were no differences among subgroups groups, which is most likely due to small sample size.

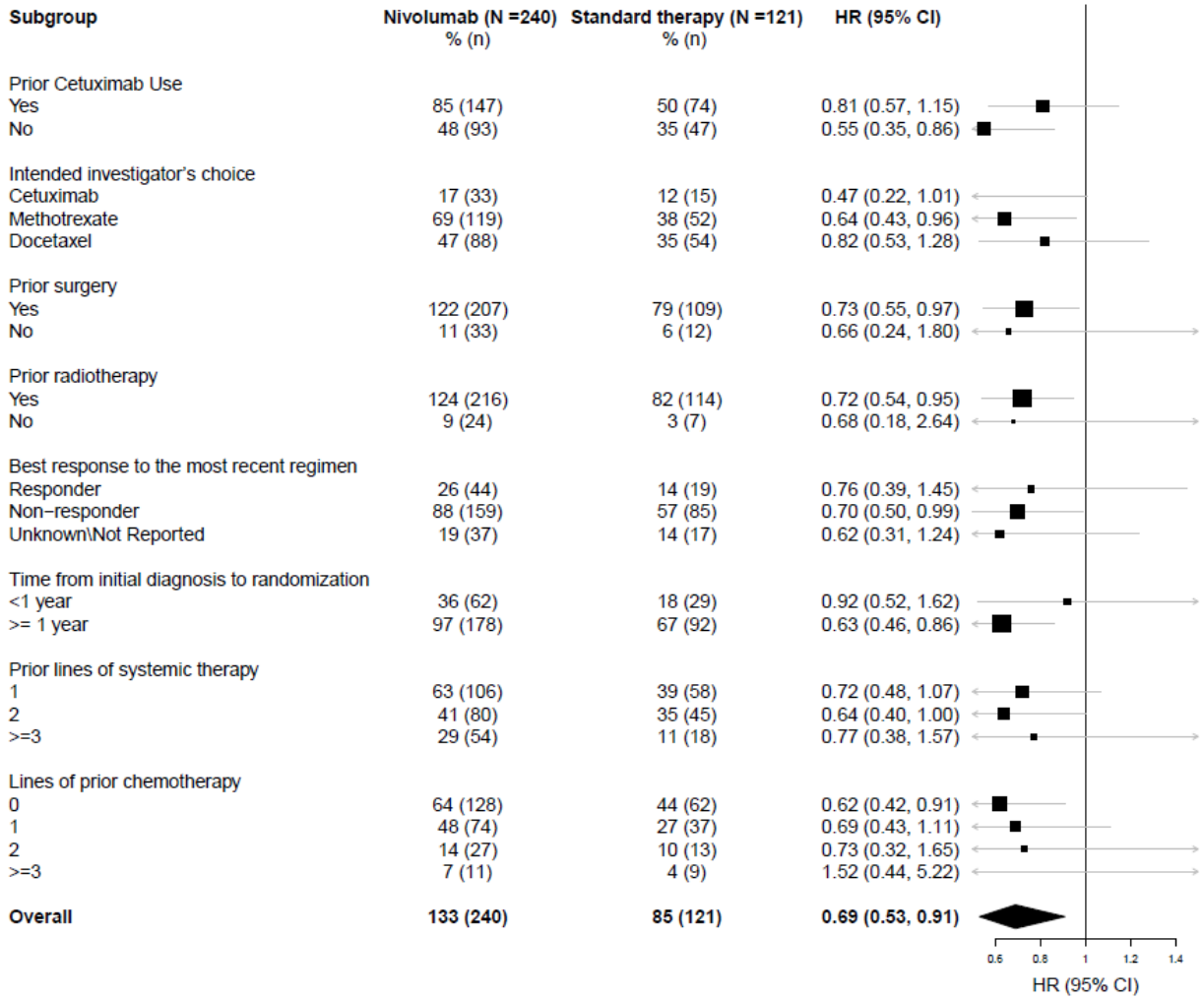
Figure 3. Subgroup analysis of overall survival stratified by age, gender, race, region, ECOG status, tobacco use, disease at entry, HPV-16 status and site of primary tumour

Subgroup	Nivolumab (N =240) % (n)	Standard therapy (N =121) % (n)	HR (95% CI)
Age			
< 65	90 (172)	54 (76)	0.64 (0.45, 0.89)
>= 65 AND < 75	35 (56)	26 (39)	0.93 (0.56, 1.54)
>= 75	8 (12)	5 (6)	
Gender			
Male	106 (197)	73 (103)	0.65 (0.48, 0.88)
Female	27 (43)	12 (18)	0.93 (0.47, 1.85)
Race			
White	115 (196)	76 (104)	0.72 (0.53, 0.96)
Black	5 (10)	1 (3)	
Asian	9 (29)	8 (14)	0.39 (0.15, 1.04)
Other	4 (5)		
Region			
North America	52 (101)	33 (44)	0.55 (0.36, 0.85)
EU	72 (109)	44 (62)	0.91 (0.62, 1.33)
ROW	9 (30)	8 (15)	0.48 (0.19, 1.26)
ECOG			
0	18 (49)	13 (23)	0.60 (0.30, 1.23)
>= 1	114 (190)	71 (97)	0.71 (0.53, 0.96)
Not Reported	1 (1)	1 (1)	
Tobacco use			
Never	20 (39)	23 (31)	0.58 (0.32, 1.06)
Current/Former	106 (191)	58 (85)	0.71 (0.52, 0.99)
Not Reported	7 (10)	4 (5)	
Disease stage at entry			
III	15 (25)	7 (10)	0.61 (0.23, 1.61)
IV	117 (214)	78 (111)	0.68 (0.51, 0.91)
Not Reported	1 (1)		
HPV−16 status			
Positive	33 (63)	20 (29)	0.56 (0.32, 0.99)
Negative	28 (50)	25 (36)	0.73 (0.42, 1.25)
Unknown	1 (2)	1 (1)	
Not Reported	71 (125)	39 (55)	0.78 (0.53, 1.16)
Site of Primary Tumor			
Larynx	22 (34)	11 (15)	0.75 (0.36, 1.59)
Oral cavity	61 (108)	51 (67)	0.73 (0.51, 1.07)
Pharynx	47 (92)	21 (36)	0.71 (0.42, 1.19)
Other	3 (6)	2 (3)	
Overall	**133 (240)**	**85 (121)**	**0.69 (0.53, 0.91)**



Source: Ferris et al, (2016). NEJM.[2]

Figure 4. Subgroup analysis of overall survival stratified by prior cetuximab use, intended investigator's choice, prior surgery and/or radiotherapy, best response to the most recent regimen, time from initial diagnosis to randomization and prior lines of systemic therapy and/or chemotherapy.



Source: Ferris et al, (2016). NEJM.[2]

The treatment subgroup analysis for overall survival is presented in Figure 4. Owing to smaller sample sizes, there were no significant differences observed across the subgroups.[2] It was noted that there was a protective effect of nivolumab as compared to methotrexate on overall survival (HR: 0.64, 95% CI: 0.43 to 0.96); however, the effect was attenuated among patients who were treated with cetuximab or docetaxel (P > 0.05 for both) (Figure 4).

The effect of tumour PD-L1 expression status on overall survival was also explored (Table 10). PD-L1 expression was only evaluated in 72.0% of patients.[2] Among these patients, 57.3% had a PD-L1 expression level greater than 1%.[2] Patients who were treated with nivolumab and who had a PD-L1 expression greater than 1% had a reduced risk of death as compared to those treated with standard therapy (HR: 0.55, 95% CI: 0.36 to 0.83).[2] This effect was not significant in patients with a PD-L1 less than 1% (HR: 0.89, 95% CI: 0.54 to 1.45). Similar effects estimates using a 5% and 10%

tumour PD-L1 expression threshold were observed (Table 10). A post-hoc analysis of tumour p16 status was also conducted among 49.3% of patients enrolled in Checkmate 141 (Table 10).[2] It was also stated that there were no significant differences between positive and negative tumour p16 status (P for interaction: 0.55).[2]

Table 10: Exploratory Analysis of Overall Survival According to Tumor PD-L1 Expression and p16 Status Subgroups

	Nivolumab*		Standard therapy *		Unstratified HR (95% CI)
	n (%)	Median survival (Months)	n (%)	Median survival (Months)	
All patients	240 (100.0)	7.5	121 (100.0)	5.1	0.69 (0.53–0.91)
PD-L1 expression level[A]					
≥1%	88 (36.7)	8.7	61 (50.4)	4.6	0.55 (0.36–0.83)
≥5%	54 (22.5)	8.8	43 (35.5)	4.6	0.50 (0.30–0.83)
≥10%	43 (17.9)	8.7	34 (28.1)	5.2	0.56 (0.31–1.01)
<1%	73 (30.4)	5.7	38 (31.4)	5.8	0.89 (0.54–1.45)
<5%	107 (44.6)	7	56 (46.3)	5.1	0.81 (0.55–1.21)
<10%	118 (49.2)	7.2	65 (53.7	4.6	0.73 (0.50–1.06)
Not quantifiable	79 (32.9)	7.8	22 (18.2)	5.8	0.79 (0.44–1.44)
p16 status[B]					
Positive	63 (26.2)	9.1	29 (24.0)	4.4	0.56 (0.32–0.99)
Negative	50 (20.8)	7.5	36 (29.8)	5.8	0.73 (0.42–1.25)

A: Expression of PD-L1 was measured in 260 patients ($N_{nivolumab}$ = 161 and $N_{Standard\ therapy}$ = 99)
B: p16 levels were measured in 178 patients ($N_{nivolumab}$ = 113 and $N_{Standard\ therapy}$ = 65)
Source: Ferris et al (2016). NEJM.[2]

Progression free survival

PFS a key secondary outcome was defined as the time between the date of randomization to the first date of documented disease progression as assessed by the study investigator using RECIST 1.1 or death due to any cause.[3] Patients who received subsequent systemic therapy prior to disease progression were censored at the last tumour assessment before starting the new therapy.[24] In order to control for type I error, a hierarchical testing approach was used and it was implemented if the overall survival effect estimate was statistically significant.[3] For the assessment of PFS, the Manufacturer used a later database lock (05-May-2016) than the interim analysis date (18-Dec-2015).[29] To account for the later database lock, the Manufacturer stated that the PFS analysis was restricted to progression events (death or radiological progressions) that occurred before the interim analysis.

In the nivolumab group, 79.2% patients died or had disease progression and the median PFS was 2.0 months (95% CI: 1.9 to 2.1).[2] In contrast, 85.1% patients in the standard therapy arm died or had progressive disease and the median PFS was 2.3 months (95% CI: 1.9 to 3.1).[2] It was reported that there was no difference between nivolumab and standard therapy on the effect of PFS (HR: 0.89, 95% CI: 0.70 to 1.13). Similar to the overall survival analysis, the Kaplan-Meier curves for PFS were also non-proportional.

As previously mentioned, patients in the nivolumab and standard therapy group had the option of being treated beyond progression, which was defined as the last dosing date after RECIST 1.1 progression.[30] There were 24.6% (n=58/236) of patients in the nivolumab group who were treated beyond progression.[30] Among these 58 patients, 15 patients were considered non-conventional benefiters. These patients had not experienced a best objective response of complete or partial response prior to the initial RECIST 1.1 defined progression

Response Rate

Table 11: Best overall response as assessed by the study investigator among patients in the Checkmate 141 Trial

Outcome	Nivolumab N = 240	Standard Therapy N = 121
Best overall response		
Complete Response, n (%)	6 (2.5)	1 (0.8)
Partial Response, n (%)	26 (10.8)	6 (5.0)
Stable Disease, n (%)	55 (22.9)	43 (35.5)
Progressive Disease, n (%)	100 (41.7)	42 (34.7)
Unable to determine, n (%)	53 (22.1)	29 (24.0)
Never treated	4 (1.7)	8 (6.6)
Wrong cancer diagnosis	0	0
Death prior to disease assessment	30 (12.5)	11 (9.1)
Early discontinuation due to toxicity	2 (0.8)	1 (0.8)
Other	15 (6.3)	8 (6.6)
Not reported	2 (0.8)	1 (0.8)
ORR, % (95% CI)[A]	13.3 (9.3, 18.3)	5.8 (2.4,11.6)
DOR, median in months (range)[B]	Not estimated	Not estimated
TTR, median in months (range)[C]	2.1 (1.8, 7.4)	2.0 (1.9, 4.6)

CR = complete response; ORR = overall response rate; DCR = disease control rate; DOR = duration of response; TTR = time to response.
A: Defined as the proportion of complete plus partial responses.
B: Defined as the between the date of first documented response (CR or PR) to the date of the first documented progression as determined by the study investigator among patients with CR or PR.
C: Defined as the time from randomization to the date of first confirmed documented response (PR or CR) as assessed by the study investigator.
Source: Module 2.7.3[29]

Overall Response Rate

ORR another secondary outcome and it was defined as the proportion of patients with the best overall response, which was measured as the sum of complete response (CR) and partial response (PR) using the RECIST 1.1.[24] Tumour assessment for best overall response was performed by the study investigator and it occurred before patients received any additional antineoplastic therapies. Moreover, patients who continued treatment beyond progression had their best overall response determined using response assessments at the time of initial RECIST 1.1 progression.[3] As previously mentioned, to control for type 1 error, a hierarchical testing approach was utilized, where the ORR would be tested in all randomized patients if PFS was significant.[3] It should be noted that the reported effect estimate of PFS was nonsignificant, and therefore, these results for

ORR should be interpreted with caution since it is unclear if they have been adjusted for multiplicity.

Patients in the nivolumab group were more likely to demonstrate an ORR as compared with those in the standard group (13.3% [95% CI, 9.3 to 18.3] vs. 5.8% [95% CI, 2.4 to 11.6]) (Table 11).[29] However, these estimates were not significantly different. The Manufacturer noted that 22.1% of patients in the nivolumab group and 24.0% of patients in the standard therapy group had a response that could not be determined.[29] Patients were most likely to have an unknown response because they died prior to disease assessment (12.5% in nivolumab vs. 9.1% in standard therapy).[29]

Duration of Response

DOR was defined as the time between the date of first documented response (CR or PR) to the date of the first documented progression as determined by the study investigator among patients with CR or PR. The Manufacturer reported that at the time of the interim analysis the DOR was not available for either treatment group.[30]

Time to Response

TTR was defined as the time from randomization to the date of first confirmed documented response (PR or CR) as assessed by the study investigator in patients with CR or PR.[3]The Manufacturer reported that the TTR was similar for patients to randomized nivolumab or standard therapy (2.1 months (range: 1.8 to 7.4) and 2.0 months (range 1.9 to 4.6), respectively).[29]

Quality of Life

The following questionnaires were used to assess PROs: EORTC QLQ-C30, QLQ-H&N35 and EQ-5D-3L. The minimal important difference (MID) for EORTC QLQ-C30 was a change in 10 points while the MID for QLQH&N35 and EQ-3D-5L was a change in 7 points.[2] Higher values on the EQ-5D-3L VAS and EORTC QLQ-C30 functional and global health/QOL scales represent an improvement while higher values on the EORTC QLQ-H&N35 indicate more symptomatology or problems.[3]

Baseline values for all questionnaires were balanced across treatment groups. In the nivolumab group, the completion rates remained near 70% until week 39.[4] On the other hand, in the standard treatment group, completion rates dropped to nearly 50% by week 15.[4] However, by week 15, there were only 35% of patients in the nivolumab group and 25% of patients in the standard therapy group.[4] To account for the small sample size, the analysis of PROs was limited to week 9 and 15 (only the first two measurements for PRO's).

Overall, in the nivolumab group, the reported PROs suggest that quality of life is at least maintained for these patients. There was minimally important decline in painkiller use reported at weeks 9, 15 and 21 and a minimally important increase in weight gain reported at weeks 9 and 15 in the EORTC QLQH&N35.[4] In contrast, there were a number of reported minimally important declines and improvements in the standard therapy group.[4] However, it is unclear whether this variability is related to the treatment or limited sample size at the different assessment periods.

This section provides an overview of the main results for the PRO questionnaires:
EQ-5D-3L:

- At week 15, a minimally important decline was observed.

EORTC QLQ-C30

- Week 9: No minimally important decline. Minimally important improvement in diarrhea.

- Week 15: a minimally important decline in physical, role, emotional, cognitive, social functioning and constipation. At the same time, a minimally important improvement in fatigue, nausea and vomiting, dyspnea, insomnia and appetite loss.

QLQH&N35
- Week 9: minimally important increase in pain, sticky saliva, nutritional supplement use, and weight gain. Minimally important decline in pain killer use.
- Week 15: minimally important increase in pain, sensory problems, trouble with social contact, sticky saliva, feeling ill, pain killer use, weight loss. Minimally important decline in feeding tube use and weight gain.

Harms Outcomes

The safety set in Checkmate 141 consisted of 236 patients in the nivolumab treatment group and 111 patients in the standard therapy group (methotrexate, n = 46; docetaxel, n = 52; and cetuximab, n = 13).[2] The database lock for safety events occurred on 18-Dec-2016.

Study Exposure

The median duration of therapy was 1.9 months for all randomized patients.[29] Among those in the standard therapy arm, the median duration of therapy was longer in patients treated with docetaxel (2 months) as compared to those treated with methotrexate or cetuximab (1.6 months).[29]

Deaths

At the interim analysis, it was reported that there were two treatment related deaths in the nivolumab group and one death in the chemotherapy group. In the nivolumab group, two patients died due to pneumonitis and hypercalcemia while one patient in the standard therapy arm died due to a lung infection.[2]

Adverse Events

Patients in the nivolumab arm reported fewer treatment-related adverse events as compared to those in the standard therapy arm (58.9% vs. 77.5%).[2] A similar pattern was observed for those reporting grade 3 or 4 events (13.1% vs. 35.1%) (Table 13) and grade 3 or 4 serious adverse events (4.7% vs, 10.8%).[2] The most frequently reported treatment-related adverse events in more than 15% of patients were fatigue (nivolumab: 14.0% and standard therapy: 17.1%), nausea (nivolumab: 8.5% and standard therapy: 20.7%) and anaemia (nivolumab: 5.1% and standard therapy: 16.2%) (Table 13).[2] There were less treatment-related adverse events leading to a discontinuation in the nivolumab group as compared to the standard therapy group (3.8% vs. 9.9%).[5]

Table 12: Treatment-related adverse events and the most frequently treatment-related adverse events that occurred in more than 15% of patients in either treatment group

Treatment-related adverse event	Nivolumab (N = 236)		Standard Therapy (N = 111)	
	Any grade	Grade 3 to 4	Any grade	Grade 3 to 4
AE	139 (58.9)	31 (13.1)	86 (77.5)	39 (35.1)
AE that led to discontinuation	9 (3.8)	6 (2.5)	11 (9.9)	7 (6.3)
SAE	16 (6.8)	11 (4.7)	17 (15.3)	12 (10.8)
Deaths	2		1	

Treatment-related adverse event	Nivolumab (N = 236)		Standard Therapy (N = 111)	
	Any grade	Grade 3 to 4	Any grade	Grade 3 to 4
Fatigue	33 (14.0)	5 (2.1)	19 (17.1)	3 (2.7)
Rash	18 (7.6)	0	5 (4.5)	1 (0.9)
Decreased appetite	17 (7.2)	0	8 (7.2)	0
Pruritus	17 (7.2)	0	0	0
Diarrhea	16 (6.8)	0	15 (13.5)	2 (1.8)
Anemia	12 (5.1)	3 (1.3)	18 (16.2)	5 (4.5)
Asthenia	10 (4.2)	1 (0.4)	16 (14.4)	2 (1.8)
Vomiting	8 (3.4)	0	8 (7.2)	0
Dry skin	7 (3.0)	0	10 (9.0)	0
Stomatitis	5 (2.1)	1 (0.4)	10 (9.0)	3 (2.7)
Weight loss	4 (1.7)	0	6 (5.4)	0
Mucosal inflammation	3 (1.3)	0	14 (12.6)	2 (1.8)
Peripheral neuropathy	1 (0.4)	0	7 (6.3)	0
Alopecia	0	0	14 (12.6)	3 (2.7)
Neutropenia	0	0	9 (8.1)	8 (7.2)
AE = adverse events Source: Module 2.5[5] and Ferris et al (2016).NEJM.[2]				

As compared to the standard therapy arm, patients treated with nivolumab were less likely to experience a treatment-related serious adverse event (6.8% vs. 15.3%).[5] The following grade 3 or 4 serious adverse events occurred more frequently in the nivolumab group as compared to standard therapy group: neoplasms benign, malignant and unspecified (3% vs. 1.8%); respiratory, thoracic, and mediastinal disorders (13.6% vs.9.9%); and metabolism and nutrition disorders (5.5% vs. 2.7%) (Table 13).[4] In contrast, patients on standard therapy were more likely to report a grade 5 serious adverse event due to neoplasms benign, malignant and unspecified as compared to those on nivolumab (20.7% vs 16.1%).[4]

Table 13: Serious adverse events that occurred in more than two patients in the CheckMate 141 Trial

Event	Nivolumab (N = 236)			Standard Therapy (N = 111)		
	Any grade	Grade 3-4	Grade 5	Any grade	Grade 3-4	Grade 5
Neoplasms benign, malignant and unspecified	47 (19.9)	7 (3.0)	39(16.5)	26(23.4)	2 (1.8)	23 (20.7)
Infections and infestations	37 (15.7)	27(11.4)	1 (0.4)	21(18.9)	17(15.3)	1 (0.9)
Respiratory, thoracic and mediastinal disorders	35 (14.8)	32(13.6)	1 (0.4)	12(10.8)	11 (9.9)	0
Metabolism and nutrition disorders	17 (7.2)	13 (5.5)	1 (0.4)	3 (2.7)	3 (2.7)	0
Gastrointestinal disorders	11 (4.7)	5 (2.1)	0	10 (9.0)	7 (6.3)	0
General disorders and administration site conditions	11 (4.7)	6 (2.5)	0	14(12.6)	6 (5.4)	0
Nervous system disorders	7 (3.0)	5 (2.1)	1 (0.4)	5 (4.5)	4 (3.6)	0
Blood and lymphatic system disorders	0	0	0	3 (2.7)	3 (2.7)	0
Source: Ferris et al (2016).NEJM.[2,4]						

For select adverse events, patients treated with nivolumab were more likely to report a skin adverse event (15.7% vs. 12.6%) or an endocrine adverse event (7.6% vs. 0.9%) as compared to patients treated with standard therapy (Table 14).[4] On the other hand, those in the standard therapy experienced more gastrointestinal adverse events (14.4% vs. 6.8%) than those treated with nivolumab.[2]

Table 14: Patients with select treatment related adverse events by treatment arm

Event	Nivolumab (N = 236)		Standard Therapy (N = 111)	
	Any grade	Grade 3-4	Any grade	Grade 3-4
Gastrointestinal	16 (6.8)	0	16 (14.4)	2 (1.8)
Hepatic	5 (2.1)	2 (0.8)	4 (3.6)	1 (0.9)
Pulmonary	5 (2.1)	2 (0.8)	1 (0.9)	0
Renal	1 (0.4)	0	2 (1.8)	1 (0.9)
Skin	37 (15.7)	0	14 (12.6)	2 (1.8)
Hypersensitivity/infusion reaction	3 (1.3)	0	2 (1.8)	1 (0.9)
Endocrine	18 (7.6)	1 (0.4)	1 (0.9)	0
Source: Ferris et al (2016).NEJM.[2,4]				

6.4 Ongoing Trials

No ongoing trials meeting the review's inclusion criteria were found.

7 SUPPLEMENTAL QUESTIONS

No supplemental questions were addressed in this review.

8 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.

9 ABOUT THIS DOCUMENT

This Clinical Guidance Report was prepared by the pCODR Head and Neck 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 nivolumab (Opdivo) for squamous cell carcinoma of the head and neck (SCCHN). 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. There was no non-disclosable information in the Clinical Guidance Report provided to pERC for their deliberations.

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.

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. There was no non-disclosable information in the Clinical Guidance Report provided to pERC for their deliberations.

APPENDIX A: LITERATURE SEARCH STRATEGY

See Appendix B for more details on literature search methods.

1. Literature search via OVID platform

Database(s): **EBM Reviews - Cochrane Central Register of Controlled Trials** January 2017, **Embase** 1974 to 2017 February 13, **Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)** 1946 to Present

Search Strategy:

#	Searches	Results
1	(Opdivo* or nivolumab* or 946414-94-4 or MDX 1106 or MDX1106 or BMS936558 or BMS 936558 or ONO4538 or ONO 4538 or 31YO63LBSN).ti,ab,kf,kw,hw,rn,nm.	4819
2	exp "Head and Neck Neoplasms"/	548013
3	(SCCHN or HNSCC or leukoplakia* or (thyroid adj3 nodule)).ti,ab,kf,kw,hw.	50887
4	((esophageal or facial or face or eyelid* or mouth or lip or lips or palatal or (salivary adj3 gland*) or tongue or otorhinolaryngologic or ear or ears or laryngeal or nose or nasal or pharyngeal or parathyroid or thyroid or tracheal) adj3 (cancer* or neoplasm* or carcinoma* or tumor or tumors or tumours* or adenocarcinoma*)).ti,ab,kf,kw,hw.	453346
5	Neoplasm, Squamous Cell/ or Carcinoma, Squamous cell/	141743
6	(cancer* or neoplasm* or carcinoma* or tumor or tumors or tumours* or adenocarcinoma*).ti,ab,kf,kw,hw.	7753916
7	5 or 6	7753916
8	(Head or neck or heads or necks or UADT or (upper adj3 aerodigestive adj3 track)).ti,ab,kf,kw,hw.	1027080
9	7 and 8	278480
10	2 or 3 or 4 or 9	821447
11	1 and 10	364

12	11 use cctr	11
13	11 use ppez	43
14	12 or 13	54
15	*Nivolumab/ or (Opdivo* or nivolumab* or MDX 1106 or MDX1106 or BMS936558 or BMS 936558 or ONO4538 or ONO 4538 or 31YO63LBSN).ti,ab,kw,hw.	4714
16	"Head and neck tumor"/	16287
17	(SCCHN or HNSCC or leukoplakia* or (thyroid adj3 nodule)).ti,ab,kw,hw.	50706
18	((esophageal or face or facial or eyelid* or mouth or lip or lips or palatal or (salivary adj3 gland*) or tongue or otorhinolaryngologic or ear or ears or laryngeal or nose or nasal or pharyngeal or parathyroid or thyroid or tracheal) adj3 (cancer* or neoplasm* or carcinoma* or tumor or tumors or tumours* or adenocarcinoma*)).ti,ab,kw,hw.	452165
19	Squamous cell carcinoma/	239134
20	(cancer* or neoplasm* or carcinoma* or tumor or tumors or tumours* or adenocarcinoma*).ti,ab,kw,hw.	7748820
21	(Head or neck or UADT or (upper adj3 aerodigestive adj3 track)).ti,ab,kw,hw.	997005
22	19 or 20	7748820
23	21 and 22	276255
24	16 or 17 or 18 or 23	681320
25	15 and 24	307
26	25 use oemezd	259
27	14 or 26	313
28	limit 27 to english language	299
29	conference abstract.pt.	2469969

30 28 and 29	40
31 limit 30 to yr="2012 -Current"	40
32 28 not 29	259
33 31 or 32	299
34 remove duplicates from 33	250

2. Literature search via PubMed

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

Search	Add to builder	Query	Items found
#13	Add	Search **#11 AND #12**	5
#12	Add	Search **publisher[sb]**	513125
#11	Add	Search **#4 AND #10**	41
#10	Add	Search **#5 OR #6 OR #9**	345343
#9	Add	Search **#7 AND #8**	80613
#8	Add	Search **Head[tiab] OR neck[tiab] OR UADT[tiab] OR upper aerodigestive track[tiab]**	360741
#7	Add	Search **Neoplasm, Squamous Cell[MeSH] OR Carcinoma, Squamous cell[MeSH] OR cancer*[tiab] OR neoplasm*[tiab] OR carcinoma*[tiab] OR tumor[tiab] OR tumors[tiab] OR tumours*[tiab] OR adenocarcinoma*[tiab]**	2513070
#6	Add	Search **((esophageal[tiab] OR face[tiab] OR facial[tiab] OR eyelid*[tiab] OR mouth[tiab] OR lip[tiab] OR lips[tiab] OR palatal[tiab] OR (salivary[tiab] AND gland*[tiab]) OR tongue[tiab] OR otorhinolaryngologic[tiab] OR ear[tiab] OR ears[tiab] OR laryngeal[tiab] OR nose[tiab] OR nasal[tiab] OR pharyngeal[tiab] OR parathyroid[tiab] OR thyroid[tiab] OR tracheal[tiab])) AND (neoplasm*[tiab] cancer[tiab] OR neoplasm[tiab] OR carcinoma[tiab] OR tumor[tiab] OR tumours[tiab] OR adenocarcinoma*[tiab])**	120249
#5	Add	Search **Head and Neck Neoplasms[MeSH] OR SCCHN[tiab] OR HNSCC[tiab] OR leukoplakia*[tiab] OR thyroid nodule*[tiab]**	274465
#4	Add	Search **nivolumab[Supplementary Concept] OR nivolumab*[tiab] OR Opdivo*[tiab] OR 946414-94-4[tiab] OR MDX 1106[tiab] OR MDX1106[tiab] OR BMS936558[tiab] OR BMS 936558[tiab] OR ONO4538[tiab] OR ONO 4538[tiab]**	965

3. **Cochrane Central Register of Controlled Trials (Central)**
   Searched via Ovid

4. **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 terms: Opdivo (nivolumab)/SCCHN

Select international agencies including:

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

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

S**earch terms: Opdivo (nivolumab)/SCCHN**

Conference abstracts:

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

Search terms: Opdivo (nivolumab)/SCCHN/ last 5 years

APPENDIX B: DETAILED METHODOLOGY OF LITERATURE REVIEW

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 (1946-2017 February 14) with Epub ahead of print, in-process records & daily updates via Ovid; Embase (1974-2017 February 13) via Ovid; The Cochrane Central Register of Controlled Trials (January 2017) 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 Opdivo (Nivolumab) and Squamous Cell Carcinoma of the Head and Neck (SCCHN).

No methodological filters were applied to limit retrieval by publication 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 June 1, 2017.

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) 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. Two members of the pCODR Methods Team independently made the final selection of studies to be included in the review and differences were resolved through discussion.

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.

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