ABSTRACT

Background In the present study, we examined real-world treatment patterns for squamous cell carcinoma of the head and neck (SCCHN) in Canada, which are largely unknown.

Methods Oncologists across Canada provided data for disease history, characteristics, and treatment patterns during May–July 2016 for 6–8 consecutive patients receiving first-line or second-line drug treatment for SCCHN (including locally advanced and recurrent or metastatic disease).

Results Information from 16 physicians for 109 patients receiving drug treatment for SCCHN was provided; 1 patient was excluded from the treatment-pattern analysis. Median age in the cohort was 63 years [interquartile range (IQR): 57–68 years], and 24% were current smokers, with a mean exposure of 26.2 ± 12.7 pack-years. The most common tumour site was the oropharynx (48%). Most patients (84%) received platinum-based regimens as first-line treatment (44% received cisplatin monotherapy). Use of cetuximab-based regimens as first-line treatment was limited (17%). Of 53 patients receiving second-line treatment, 87% received a first-line platinum-based regimen. Median time between first-line treatment with a platinum-based regimen and initiation of second-line treatment was 55 days (IQR: 20–146 days). The most common second-line regimen was cetuximab monotherapy (43%); platinum-based regimens were markedly infrequent (13%).

Conclusions Our analysis provides real-world insight into SCCHN clinical practice patterns in Canada, which could inform reimbursement decision-making. High use of platinum-based regimens in first-line drug treatment was generally reflective of treatment guidelines; cetuximab use in the second-line was higher than anticipated. Additional real-world studies are needed to understand the effect of novel therapies such as immuno-oncology agents on clinical practice and outcomes, particularly for recurrent or metastatic SCCHN.

Key Words Canada, cetuximab, head-and-neck cancer, platinum-based therapy, recurrent disease, metastatic disease, squamous cell carcinoma, SCCHN, treatment patterns

INTRODUCTION

Head-and-neck cancers encompass neoplasms of the oral cavity, pharynx, larynx, sinuses, and salivary glands. In 2012, approximately 686,000 new cases of head-and-neck cancer and 376,000 associated deaths occurred worldwide, representing the 7th leading cancer by incidence, with squamous cell carcinoma of the head and neck (SCCHN) accounting for approximately 90% of those cancers. An estimated 4700 Canadians were diagnosed with oral cancer in 2017, resulting in 1250 deaths. The most recent Canadian statistics for oropharyngeal cancer reported 180 new cases and 131 deaths in 2013.

Treatment for SCCHN depends on stage at diagnosis: Patients diagnosed early are treated with curative intent; patients diagnosed at advanced stages or with recurrent or metastatic disease (R/M SCCHN) are treated with the aim of prolonging remission. Because of limited therapeutic options, R/M SCCHN poses a treatment challenge—particularly for the patients who present with advanced-stage disease...
clinical practice patterns and clinical outcomes is needed to inform reimbursement decision-makers about treatment options in patients with scchn. The objective of the present study was therefore to identify real-world treatment patterns for patients with scchn so as to better understand the standard of care, including by line of therapy, in Canadian clinical practice.

METHODS

Study Design
This descriptive cross-sectional analysis used survey data collected from 2 May to 18 July 2016 from participating medical oncologists actively involved in the management of scchn across Canada. Details of the survey method, which has been used in more than 50 disease areas, have previously been published. Eligible physicians who wanted to participate in the study were identified from public listings and were required to have qualified as a medical oncologist between 1981 and 2013 and to be treating a minimum of 10 patients with scchn per month. Participating physicians completed a detailed electronic Patient Record Form reporting data for their next 6–8 consecutively treated patients who met these eligibility criteria: scchn diagnosis, 18 years of age or older, receiving active drug treatment for scchn, not enrolled in a clinical trial (at the time of consultation), and primary tumour not located on a salivary gland or the nasopharynx. Excluded from the study were patients receiving best supportive care; those undergoing either surgery or radiotherapy (or both), but no active drug treatment; and those under a “watch and wait” treatment approach. Proportional quota sampling was used to generate a quasi-random sample evenly split between patients who were receiving first-line active drug treatment and those who were receiving second-line or later active drug treatment at the point of data collection.

Data Collection
Information extracted from the electronic Patient Record Forms included demographic and clinical characteristics of the patients and complete scchn drug and non-drug treatment history (including surgery and radiotherapy). Real-world treatment patterns identified in clinical practice for the participating providers included comprehensive treatment history from diagnosis to current treatment and treatment modality sequencing (that is, surgery, radiotherapy, chemotherapy, and targeted therapy, including specific agents received).

The end of a given line of drug therapy was defined by the addition, switching, or discontinuation of a drug or by repeat of the same therapy after completion of the original course. A change in dose or a treatment holiday was not considered a new line of therapy. Line of treatment was counted relative to each patient’s first-line active drug treatment (either monotherapy or a combination regimen) with or without concurrent radiotherapy and regardless of disease progression (that is, for patients who had previously received drug therapy for non-recurrent or metastatic disease). Drug treatment for subsequent recurrent or metastatic disease was not considered “first line” for that disease.
stage. For the purposes of the present study, radiotherapy alone and surgery alone were not counted as lines of treatment. Best supportive care was considered a line of therapy only in the third line or later. The length of time between diagnosis and treatment initiation, the duration of first-line therapy, and the time to initiation of second-line therapy also were recorded for patients receiving drug treatment.

**Statistical Analyses**
Demographics, clinical characteristics, and antineoplastic treatment patterns are described using frequencies and proportions for categorical data and using means with standard deviation or medians with interquartile range (IQR) for numeric data. Time variables are reported as medians with IQR. The probability of time to progression from initiation of first-line therapy until initiation of second-line therapy was plotted using the Kaplan–Meier method and was calculated using the initiation dates of first-line and second-line therapy. The time-to-progression analysis included all patients in the sample, including those receiving first-line therapy only, who were censored at the time of data collection.

**RESULTS**

**Demographic and Clinical Characteristics of the Patients**
Data from 16 physicians for 109 patients with scchn receiving first-line or second-line drug treatment were obtained. The treatment pattern analysis (n = 108) excluded 1 patient whose treatment data were incomplete. Most patients (77%) were diagnosed either by a head-and-neck or ear/nose/throat surgeon (55%) or by a medical oncologist (22%). On average, patients saw a medical oncologist 6.7 times and a radiation oncologist 6.1 times annually. Most patients were receiving treatment as part of a provincial or territorial health insurance plan (75%). Participating patients were drawn predominantly from clinics in Ontario (30% of patients), Quebec (29%), and Alberta (17%).

Median patient age in the cohort was 63 years (IQR: 57–68 years), and 72% of the patients were men. Median time from diagnosis to the point of data capture was 244 days (IQR: 124–656 days). Of the 109 patients included in the study, 90% were current or former smokers, and the mean smoking exposure for the current smokers was 26.2 ± 12.7 pack-years. The most common primary tumour site was the oropharynx (48%). At the point of data capture, 76% of patients had locoregionally advanced disease (stages I–IVB), and 23% had recurrent or metastatic disease (stage IVc). Compared with their counterparts having stages I–IVB disease, patients with stage IVc disease at data capture were more likely to be treated with the aim of improving quality of life (60% vs. 41%) and symptom control (44% vs. 28%), and less likely to be treated with the aim of improving os (32% vs. 46%). Similarly, when physicians were asked to predict the likely next treatment step, patients with stage IVc disease were deemed more likely to progress to best supportive care (40% vs. 11%) and less likely to continue with current treatment (32% vs. 46%). At data capture, almost two thirds of the patients (64%) were clinically fit, with an Eastern Cooperative Oncology Group performance status of 0 or 1. Of the 73 patients who underwent p16 testing to determine their human papillomavirus infection status at the point of data capture, 45% tested positive (Table 1).

**TABLE I** Demographics and clinical characteristics of the 109 study patients

| Characteristic            | Value |
|---------------------------|-------|
| Dx to data capture (days) |       |
| Median                    | 244   |
| IQR                       | 124–656 |
| Age (years)               |       |
| Median                    | 63    |
| IQR^6                     | 57–68 |
| Age group [n (%)]         |       |
| ≤70 Years                 | 92 (84) |
| >70 Years                 | 17 (16) |
| Sex [n (%)] men           |       |
| Ontario                   | 33 (30) |
| Quebec                    | 32 (29) |
| Alberta                   | 19 (17) |
| Other                     | 25 (23) |
| Diagnosing physician [n (%)] |       |
| Medical oncologist        | 24 (22) |
| Radiation oncologist      | 8 (7)  |
| HN or ENT surgeon         | 60 (55) |
| Pathologist               | 2 (2)  |
| Primary care physician    | 12 (11) |
| Other specialist (unspecified) | 2 (2)  |
| Not reported              | 1 (1)  |
| Health insurance type [n (%)] |       |
| Provincial or territorial plan | 82 (75) |
| Employer-sponsored plan   | 18 (17) |
| Private plan              | 5 (5)  |
| None, other, or unknown   | 4 (4)  |
| Smoking status [n (%)]    |       |
| Current                   | 26 (24) |
| Former                    | 72 (66) |
| Never                     | 11 (10) |
| Cigarettes per day^4 [n (%)] |       |
| <20                       | 11 (42) |
| ≥20                       | 12 (46) |
| Don’t know                | 3 (12) |
| Exposure (mean pack-years) |       |
| 26.2±12.7                 |       |
| Primary site [n (%)]      |       |
| Oropharynx                | 52 (48) |
| Oral cavity (including tongue) | 30 (28) |
| Hypopharynx               | 11 (10) |
| Larynx                    | 8 (7)  |
| Lip                       | 4 (4)  |
| Not reported              | 4 (4)  |
SCCHN Treatment Overview

Median time from diagnosis to treatment initiation was 49 days (IQR: 24–131 days). At the point of data capture, 51% of the patients were receiving first-line drug treatment, 42% were receiving second-line treatment, and 6% were receiving third-line treatment (Table II).

First-Line Drug Treatment Patterns

Of the 108 patients who received first-line therapy, most (84%, n = 91) received a platinum-based regimen as first-line treatment (Table III), and of those patients, 26% (n = 24) received concomitant radiotherapy. The individual regimen most frequently received was cisplatin monotherapy (44%, n = 48), and of those patients, 33% (n = 16) received concomitant radiotherapy. Use of cetuximab-based regimens as first-line treatment was limited (17%). Use of the extreme regimen (cisplatin–cetuximab or carboplatin–cetuximab plus 5FU)19 as first-line therapy was very rare (1%); however, 6% of the patients received extreme plus docetaxel. Docetaxel-containing regimens without cetuximab were received by 15 patients (14%), with 2 patients receiving docetaxel monotherapy.

Second-Line Drug Treatment Patterns

Median time to progression from initiation of first-line therapy to initiation of second-line therapy was 8.9 months (95% confidence interval: 6.4 months to 11.1 months; Figure 1). For the 53 patients who received second-line treatment, platinum-based therapies were used less frequently (13%) than they had been in the first line (Table IV). Few patients received concomitant radiotherapy during second-line therapy (n = 2). The oncologists reported a median of 49 days (IQR: 19–149) between the end of first-line and the initiation of second-line drug treatment (Table II). The second-line regimens most commonly used were cetuximab (43%), docetaxel (13%), paclitaxel (13%), and methotrexate (8%) monotherapies. Use of the extreme regimen remained low (2%). Of the patients who received second-line treatment, 87% (n = 46) had received a...
first-line platinum-based regimen. The median time between initiation of first-line treatment with a platinum-based regimen and initiation of second-line treatment was 55 days (iqr: 20–146 days; Table ii). Nearly half the patients previously treated with platinum-based therapy (46%) received cetuximab monotherapy; 13% received docetaxel monotherapy; 13%, paclitaxel monotherapy; 9%, methotrexate monotherapy; and 9%, another platinum-based regimen. In the patients who received platinum-based therapy in the first-line setting and who went on to receive second-line therapy, cetuximab monotherapy was the most frequently used regimen (45%, Table v).

**TABLE III** First-line drug treatment patterns in 108 patients

| Treatment regimens | With radiotherapy [n (%)] | Overall |
|--------------------|---------------------------|---------|
|                    | No            | Yes     |         |
| Carboplatin        | 2 (2)         | —       | 2 (2)   |
| Carboplatin-docetaxel | —            | 1 (1)   | 1 (1)   |
| Carboplatin-docetaxel–5FU | —            | 1 (1)   | 1 (1)   |
| Carboplatin–5FU    | 1 (1)         | —       | 1 (1)   |
| Carboplatin–paclitaxel | 1 (1)        | —       | 1 (1)   |
| Cetuximab          | 5 (5)         | 2 (2)   | 7 (6)   |
| Cisplatin          | 32 (30)       | 16 (15) | 48 (44) |
| Cisplatin–cetuximab| 3 (3)         | —       | 3 (3)   |
| Cisplatin–docetaxel–cetuximab | 1 (1)        | —       | 1 (1)   |
| Cisplatin–docetaxel–5FU | 7 (6)        | 3 (3)   | 10 (9)  |
| Cisplatin–5FU      | 5 (5)         | 1 (1)   | 6 (6)   |
| Cisplatin–5FU–cetuximab | —            | 1 (1)   | 1 (1)   |
| Cisplatin–5FU–methotrexate | 1 (1)      | —       | 1 (1)   |
| Cisplatin–other    | 1 (1)         | —       | 1 (1)   |
| Cisplatin–paclitaxel| 1 (1)        | —       | 1 (1)   |
| Docetaxel          | 2 (2)         | —       | 2 (2)   |
| Docetaxel–5FU      | —             | 1 (1)   | 1 (1)   |
| 5FU–other          | 1 (1)         | —       | 1 (1)   |
| Gemcitabine        | 1 (1)         | 1 (1)   | 2 (2)   |
| Methotrexate       | 2 (2)         | 1 (1)   | 3 (3)   |
| Other              | —             | 1 (1)   | 1 (1)   |

**Regimen class**

| Platinum-based | 67 (62) | 24 (22) | 91 (84) |
| Cetuximab-based | 14 (13) | 4 (4)   | 18 (17) |

Not mutually exclusive; regimen classes overlap. “Other” regimen assumed not to contain platinum or cetuximab.

5FU = 5-fluorouracil.

**DISCUSSION**

Treatment patterns observed in this study generally reflected current treatment guidelines reported for Canada8,20,27, with some notable deviations. Platinum-based chemotherapy (used concomitantly or postoperatively with radiotherapy) is considered the standard of care for the primary treatment of most patients with locally advanced (stages iii–ivb) scchn27. Most patients (84%) received platinum-based therapies in the first-line setting. According to international guidelines9, patients with an Eastern Cooperative Oncology Group performance status of 2 or greater should generally receive first-line monotherapy; accordingly, 6% of patients received cetuximab; 3%, methotrexate; and 2%, docetaxel. No patient received paclitaxel, carboplatin, 5fu, or capecitabine monotherapy. Docetaxel–cisplatin–5fu was received by 9% of the patients receiving first-line drug therapy. For larynx preservation, Canadian guidelines recommend either that regimen followed by radiation and surgery, or concurrent chemoradiotherapy, in preference to radiotherapy alone27. Cetuximab (as monotherapy or in combination with other agents) was received by 17% of patients in the first line; practice guidelines suggest the use of cetuximab in addition to intensified radiotherapy as an alternative to chemoradiotherapy for patients with stages iii–ivb scchn who are ineligible for concurrent platinum-based chemotherapy or those more than 70 years of age27.

Use of the extreme regimen19 was low, with only 1% of patients receiving the regimen in the first line, and only 2% receiving it in the second line, although an additional 6% of patients received extreme–docetaxel as first-line treatment. Based on observations of increased survival18,
Canadian practice guidelines recommend the extreme regimen to improve survival and response rate in "suitable" untreated patients with r/m SCCN\textsuperscript{20,21}. However, few patients in the present study had metastatic disease at diagnosis. Additionally, extreme and other existing platinum-based treatment options are associated with severe toxicity and adverse effects on health-related quality of life\textsuperscript{28}. It is unclear whether the low rates of use of extreme or other cetuximab–platinum–5FU–containing regimens observed in our study reflect such concerns.

Optimal first-line treatment selection is crucial to ensure that patients remain sufficiently healthy to receive subsequent treatments (that is, second-line and beyond)\textsuperscript{18},—particularly those with locoregional progression. In the present study, second-line drug treatment regimens varied and primarily used monotherapies—namely, cetuximab (43%), taxanes (docetaxel, 13%; paclitaxel, 13%), and methotrexate (8%). Of the patients who progressed to second-line treatment, a high proportion (87%) had received platinum-based first-line treatment; only 9% of patients who received first-line platinum-based therapy subsequently received platinum-based therapy in the second-line setting. Given the poor response rates with existing therapies for r/m SCCN and disease progression during or after platinum-based chemotherapy\textsuperscript{18}, the substantial health care and economic burden represented by those patients is driven largely by hospitalizations and anticancer therapy costs\textsuperscript{10,28}. That observation has led to suggestions to limit the use of combination regimens for metastatic cancers and to restrict chemotherapy on the basis of performance status\textsuperscript{30}.

Higher-than-expected cetuximab use was identified in the second line. A formal comparison of observed treatment patterns with guideline recommendations was not the purpose of our study, because guidelines might not reflect currently approved indications or preferred clinical practice in a given country. Additionally, physician prescribing preferences are likely to be influenced by familiarity and personal preferences. For example, chemotherapy often incorporates a combination of drugs, each of which might have already been on the market for a long time. The label might therefore not reflect the combinations used for the treatment of cancer in a particular setting, oncologists might individualize therapy, and institutional protocols might allow for flexibility. The practice patterns identified in the present study illustrate the importance of real-world evidence in describing clinical practice and informing reimbursement decision-makers.

The increasing availability of novel therapies with better adverse event profiles could potentially change the Canadian treatment algorithm for SCCN. A new therapy class—immune checkpoint inhibitors—has shown promising results as monotherapy, with tolerable toxicities\textsuperscript{31–34} and improvements in health-related quality of life\textsuperscript{32,35} in patients with r/m SCCN. However, our analysis was conducted before Canadian approval of those therapies. Subsequent real-world treatment-pattern studies are needed to understand the effects of novel therapies on clinical

### TABLE IV  Second-line drug treatment patterns in 53 patients

| Treatment | With radiotherapy [n (%)] | Overall |
|-----------|--------------------------|---------|
|           | No | Yes | |
| **Treatment regimens** | | | |
| Capecitabine–cetuximab | 1 (2) | — | 1 (2) |
| Carboplatin | 1 (2) | — | 1 (2) |
| Carboplatin–5FU | 1 (2) | — | 1 (2) |
| Carboplatin–paclitaxel | — | 1 (2) | 1 (2) |
| Cetuximab | 22 (42) | 1 (2) | 23 (43) |
| Cisplatin | 1 (2) | — | 1 (2) |
| Cisplatin–5FU | 2 (4) | — | 2 (4) |
| Cisplatin–5FU–cetuximab | 1 (2) | — | 1 (2) |
| Docetaxel | 7 (13) | — | 7 (13) |
| Docetaxel–cetuximab | 1 (2) | — | 1 (2) |
| Erlotinib | 2 (4) | — | 2 (4) |
| 5FU | 1 (2) | — | 1 (2) |
| Methotrexate | 4 (8) | — | 4 (8) |
| Paclitaxel | 5 (9) | — | 7 (13) |
| **Regimen classes** | | | |
| Platinum-based regimens | 6 (11) | 1 (2) | 7 (13) |
| Cetuximab-based regimens | 25 (47) | 1 (2) | 26 (49) |

\* Not mutually exclusive; regimen classes overlap.
5FU = fluorouracil.

### TABLE V  Second-line treatment in 46 patients receiving first-line platinum

| Treatment Value | [n (%)] |
|-----------------|---------|
| **Monotherapy** |         |
| Cetuximab | 20 (43) |
| Cetuximab + RT | 1 (2) |
| Docetaxel | 6 (13) |
| Docetaxel + RT | 0 |
| 5FU ± RT | 1 (2) |
| Gemcitabine ± RT | 0 |
| Methotrexate | 4 (9) |
| Methotrexate + RT | 0 |
| Paclitaxel | 4 (9) |
| Paclitaxel + RT | 2 (4) |
| Other ± RT | 2 (4) |
| Platinum | 2 (4) |
| Platinum + RT | 0 |
| **Combination therapy** |         |
| EXTREME regimen\textsuperscript{a} ± RT | 1 (2) |
| Platinum–5FU ± RT | 0 |
| Platinum–taxane ± RT | 1 (2) |
| Other ± RT | 2 (4) |

\* Platinum–5FU–cetuximab.
5FU = fluorouracil; RT = radiotherapy.
practice and the outcomes of patients with R/M SCCN and platinum-refractory disease. To the best of the authors’ knowledge, few studies have examined real-world treatment patterns for patients with SCCN. A real-world study of patients with R/M SCCN conducted between 2006 and 2013 in the Netherlands provided insight into local drug usage patterns10; however, its reported findings cannot be compared directly with our results because of geographic differences in treatment guidelines, clinical practice, and reimbursement policies. The SCCN treatment patterns presented here provide the most reliable evidence of Canadian clinical practice to date.

Several study limitations should be noted. With respect to the study’s methods and the selection of participating physicians, a cross-sectional rather than a longitudinal approach was taken; the data therefore reflect the population with SCCN at the time of data collection and cannot be used for causal inference or to project treatment patterns beyond the reporting period, because new agents have become available and clinical practice patterns could have changed. In addition, although some data were available at the time of diagnosis, most of the included data were available only at the time of capture; the study findings might therefore not have reflected the comprehensive clinical or treatment characteristics of the patients at the time of diagnosis. Furthermore, although disease stage and treatment could be identified at data capture, we could not elucidate the disease stage of the patients during prior lines of therapy. Physician inclusion was influenced by willingness to participate, resulting in a convenience sample that might not be representative of the overall population of Canadian physicians treating patients with SCCN. In terms of patient selection, the patients included in the study represent a quasi-random sample because physicians were asked to select, from study initiation, the first 6–8 consecutive patients meeting the entry criteria. Providers were more likely to collect data from patients seen more frequently, who thus might have been overrepresented. Additionally, physician preferences could, in part, be influenced by provincial variations in reimbursement policy and patient access to relevant clinical trials. However, the systematic approach to recruitment was designed to reduce selection bias. No formalized diagnostic checklist was mandated in the study methods; instead, diagnosis of the target patient group was based on the judgment and diagnostic skills of the responding physicians, as being reflective of routine real-world clinical practice. With regard to treatment data, patients were selected on the basis of receiving drug therapy and only general first-line and second-line drug treatments were included. Information such as dose, frequency of therapy, or receipt of therapy by stage or tumour site was not reported. In addition, the classifications used in our analysis for line of therapy were based on receipt of drug therapy rather than on receipt of any therapy (for example, surgery or radiation) and could be open to interpretation. Consequently, it is not possible to differentiate between “line of any type of therapy” (that is, drug or non-drug treatment) and “line of drug therapy.” Finally, as in any study based on chart review, data quality relied on the accurate reporting of information by physicians.

CONCLUSIONS

The published literature contains little information about clinical practice patterns in SCCN. This Canadian real-world study revealed high use of platinum-based regimens as first-line treatment. Although some variation in second-line treatment patterns was noted, cetuximab-based regimens were used most frequently. Monotherapies were used more often in the second-line than in the first-line setting, with cisplatin being the monotherapy in highest use in the first line, and cetuximab being the most common monotherapy agent in the second line. The study findings generally support the view that there is no standard second-line treatment for SCCN in Canada. Management strategies are expected to evolve with the emergence of the new immuno-oncology treatment options for patients with SCCN, which could lead to improved outcomes for patients in Canada.

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CONFLICT OF INTEREST DISCLOSURES

We have read and understood Current Oncology’s policy on disclosing conflicts of interest, and we declare the following interests: KB and PH were employees of Adelphi Real World at the time of the study; AATM is a full-time employee of Bristol–Myers Squibb Canada; AM is a full-time employee of Bristol–Myers Squibb Canada and received nonfinancial support from Bristol–Myers Squibb during the conduct of the study; JWS is a full-time employee and stockholder of Bristol–Myers Squibb.

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REFERENCES

1. Wissinger E, Griebisch I, Lungershausen J, Foster T, Pashos CL. The economic burden of head and neck cancer: a systematic literature review. Pharmacoconomics 2014;32:865–82.
2. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 2015;136:E359–86.
3. Vigneswaran N, Williams MD. Epidemiologic trends in head and neck cancer and aids in diagnosis. Oral Maxillofac Surg Clin North Am 2014;26:123–41.
4. Canadian Cancer Society. Oral cavity cancer statistics [Web page]. Toronto, ON: Canadian Cancer Society; 2017. [Available at: http://www.cancer.ca/en/cancer-information/cancer-type/oral/statistics/?region=on; cited 25 September 2017]
5. Canadian Cancer Society Advisory Committee. Pharyngeal cancer statistics: Oropharyngeal cancer incidence and mortality [Web page]. Toronto, ON: Canadian Cancer Society; 2017. [Available at: http://www.cancer.ca/en/cancer-information/cancer-type/oropharyngeal/statistics/?region=on; cited 25 September 2017]
6. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Head and Neck Cancers.
TREATMENT PATTERNS FOR HEAD-AND-NECK SCC IN CANADA, Byrne et al.

Ver. 1.2017. Fort Washington, PA: nccn; 2017. [Current version available online at: https://www.nccn.org/professionals/physician_gls/f_guidelines.asp (free registration required); cited 1 June 2017]

7. Cognetti DM, Weber RS, Lai SY. Head and neck cancer: an evolving treatment paradigm. Cancer 2008;113(suppl): 1911–32.

8. Gilbert R, Devries-Aboud M, Winquist E, Waldron J, McQueen M on behalf of the Head and Neck Cancer Disease Site Group. The Management of Head and Neck Cancer in Ontario. Toronto, ON: Cancer Care Ontario; 2009. [Available online at: https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/536; cited 8 June 2017]

9. Gregoire V, Lefebvre JL, Licitra L, Felip E on behalf of the French Gastro-Intestinal and Head and Neck Group. Squamous cell carcinoma of the head and neck: ENSO-ESMO-EFRO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 2010;21(suppl 5):v184–6.

10. van der Linden N, Buter J, Pescott CP, et al. Treatments and costs for recurrent and/or metastatic squamous cell carcinoma of the head and neck in the Netherlands. Eur Arch Otorhinolaryngol 2016;273:455–64.

11. Zibelman M, Mehra R. Overview of current treatment options and investigational targeted therapies for locally advanced squamous cell carcinoma of the head and neck. Am J Clin Oncol 2016;39:396–406.

12. Echarri MJ, Lopez-Martin A, Hitt R. Targeted therapy in static or recurrent squamous cell carcinoma of the head and neck. Front Oncol 2016;6:pi1:1–5.

13. Verma TB, Blumenschein G Jr, Yuen JY, et al. Antitumor activity of pembrolizumab for treatment of recurrent or metastatic squamous cell carcinoma of the head and neck. JAMA Oncol 2017;3:1350–5. [Available online at: https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm528920.htm; cited 25 April 2017]

14. Seiwert TY, Burtness B, Mehra R, Blumenschein G Jr, et al. Nivolumab plus ipilimumab in patients with recurrent or metastatic squamous cell carcinoma of the head and neck. Lancet Oncol 2016;17:1036–45. [Available online at: https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm515627.htm; cited 25 April 2017]

15. Head and Neck Cancer Disease Site Group. 2019 Update on treatment of head and neck cancer. Curr Oncol 2019;26(2):e174.

16. Chow LQ, Haddad R, Gupta S, et al. Antitumor activity of pembrolizumab in biomarker-unselected patients with recurrent and/or metastatic head and neck squamous cell carcinoma: results from the phase 1b KEYNOTE-012 expansion cohort. J Clin Oncol 2016;34:3838–45.

17. Ferris RL, Blumenschein G Jr,业态 J, et al. Nivolumab for recurrent squamous-cell carcinoma of the head and neck. N Engl J Med 2016;375:1856–67.

18. Mehra R, Seiwert TY, Mahipal A, et al. Efficacy and safety of pembrolizumab in recurrent/metastatic head and neck squamous cell carcinoma: pooled analyses after long-term follow-up in KEYNOTE-012. J Clin Oncol 2018;36:749–55.

19. Seiwert TY, Burtness B, Mehra R, et al. Safety and clinical activity of pembrolizumab for treatment of recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-012): an open-label, multicentre, phase 1b trial. Lancet Oncol 2016;17:1036–45.

20. Harrington KJ, Ferris RL, Blumenschein G Jr, et al. Nivolumab versus standard, single-agent therapy of investigator’s choice in recurrent or metastatic squamous cell carcinoma of the head and neck (CheckMate 141): health-related quality-of-life results from a randomised, phase 3 trial. Lancet Oncol 2017;18:1104–15.