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Impact of nivolumab vs standard, single-agent therapy of investigator's choice on patient-reported outcomes in recurrent or metastatic squamous cell carcinoma of the head and neck: health-related quality-of-life results from CheckMate 141, a randomized, phase 3 trial

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Summary

Background—Patients with platinum-refractory recurrent or metastatic (R/M) squamous cell carcinoma of the head and neck (SCCHN) have limited treatment options and poor prognosis. Nivolumab significantly improved survival of this patient population when compared with standard single-agent therapy of investigator's choice (IC) in Checkmate 141; here we report the impact of nivolumab on patient-reported outcomes (PROs).

Methods—CheckMate 141 (NCT02105636) was a randomised, open-label, phase 3 trial in patients with R/M SCCHN who progressed within 6 months after platinum-based chemotherapy. Patients were randomised 2:1 to nivolumab 3 mg/kg every 2 weeks (n=240) or IC (n=121) of methotrexate (40–60 mg/m² of body surface area), docetaxel (30–40 mg/m²), or cetuximab (250 mg/m² after a loading dose of 400 mg/m²). On 26 January 2016, the independent data monitoring committee reviewed the data at the planned interim analysis and declared overall survival superiority for nivolumab over IC therapy (primary endpoint; described previously). The protocol was amended to allow patients in the IC arm to cross over to nivolumab. All patients not on active therapy are being followed for survival. As an exploratory endpoint, PROs were assessed at baseline, week 9, and every 6 weeks thereafter using the European Organisation for the Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire–Core 30 (QLQ-C30), the EORTC head and neck cancer–specific module (EORTC QLQ-H&N35), and the three-level European Quality of Life–5 Dimensions (EQ-5D) questionnaire. Differences within and between treatment arms in PROs were analysed by analyses of covariance (ANCOVA) among patients with baseline and 1 other assessment (n=129). Among all randomised patients (N=361), median time to clinically meaningful deterioration was analysed by Kaplan-Meier methods.

Findings—Treatment with nivolumab resulted in adjusted mean changes from baseline to week 15 ranging from –2.1 to +5.4 across functional and symptom domains measured by the EORTC QLQ-C30, with no domains indicating clinically meaningful deterioration. In contrast, 8 (53%) of the 15 domains in the IC arm demonstrated clinically meaningful deterioration (10 points or more) at week 15 (change from baseline range, –24.5 to +2.4). Similarly, on the EORTC QLQ-H&N35, clinically meaningful worsening at week 15 was seen in 0 domains in the nivolumab arm and 8 (44%) of 18 domains in the IC arm. Patients in the nivolumab arm experienced a clinically meaningful improvement (according to a difference of 7 points or greater) in adjusted mean

change from baseline to week 15 on the EQ-5D visual analogue scale, in contrast to a clinically meaningful deterioration in the IC arm (+7.3 vs -7.8). Differences between arms were statistically significant and clinically meaningful at weeks 9 and 15 in favour of nivolumab for role functioning, social functioning, fatigue, dyspnoea, and appetite loss on the EORTC QLQ-C30 and pain and sensory problems on the EORTC QLQ-H&N35. Median time to deterioration was significantly longer with nivolumab vs IC for 13 (37%) of 35 domains assessed across the three questionnaires.

Interpretation—In this exploratory analysis of CheckMate 141, nivolumab stabilised symptoms and functioning from baseline to weeks 9 and 15, whereas IC led to clinically meaningful deterioration. Nivolumab delayed time to deterioration of patient-reported quality-of-life outcomes compared with single-agent therapy of IC in patients with platinum-refractory R/M SCCHN. Given the significant unmet need in this population and the importance of maintaining or improving quality of life for patients with R/M SCCHN, these data support nivolumab as a new standard-of-care option in this setting.

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Introduction

Squamous cell carcinoma of the head and neck (SCCHN), including cancers of the oral cavity, pharynx, and larynx, and its treatment have a significant impact on patient quality of life (QoL).¹ Damage to anatomic structures involved in speech, swallowing, and breathing can be caused by the tumour itself or can occur as the result of surgical resection and/or chemoradiotherapy.² Consequently, alterations to basic physical functions, physical appearance, and social interactions are common among patients with SCCHN.³ Patients with SCCHN have been shown to bear greater psychological distress than those with many other cancer types because of treatment-related facial disfigurement or impaired speech, breathing, eating, or drinking.⁴

In addition to negative effects on QoL, patients with recurrent or metastatic (R/M) SCCHN have a dismal prognosis. The median overall survival (OS) for patients who progress after platinum therapy for primary or recurrent disease is 6 months or less.^{5,6} Patient-reported outcomes (PROs) have been collected to assess QoL in a limited number of clinical trials of chemotherapy and targeted therapies in R/M SCCHN, few of which have demonstrated improvements or significant differences between treatment arms.^{7–10} However, baseline QoL scores have been reported to be independent prognostic factors for OS in patients with R/M head and neck cancer.¹¹ Therefore, there is a large unmet medical need for treatments that improve prognosis as well as preserve and maximise QoL.

As SCCHN recurrence and metastasis are enabled by tumour immune evasion, mediated in part by the T cell-suppressive programmed death (PD)-1 immune checkpoint, PD-1 inhibitors are of clinical interest in this setting. Nivolumab is a fully human IgG4 PD-1 inhibitor antibody that disrupts PD-1-mediated signalling to restore antitumour immunity. This strategy has been shown to be clinically effective in a variety of solid tumour types, including SCCHN.^{12–16}

In CheckMate 141, nivolumab demonstrated improved OS compared with single-agent therapy of investigator's choice (IC) in patients with R/M SCCHN.¹⁶ The median OS was 7.5 months (95% confidence interval [CI] 5.5–9.1) with nivolumab and 5.1 (4.0–6.0) months with IC. The estimated 1-year survival rate was more than doubled with nivolumab compared with IC (36.0% vs 16.6%). Grade 3 or 4 treatment-related adverse events occurred in 13.1% of patients treated with nivolumab compared with 35.1% of those treated with IC. Moreover, a preliminary analysis of PROs showed that nivolumab stabilised QoL, in contrast to clinically meaningful deterioration observed in patients treated with IC. Here, we report the full QoL analysis based on three widely used, validated PRO questionnaires completed by patients in the CheckMate 141 study.

Methods

Study design and participants

CheckMate 141 was an international, phase 3, randomised, open-label study designed to investigate whether nivolumab improves survival in patients with platinum-refractory R/M SCCHN compared with single-agent therapy of IC. Patients were randomly assigned to treatment from 29 May 2014 to 31 July 2015, at 66 sites in 15 countries in North America, Asia, Europe, and South America (appendix p 2). Full details of the study design were previously reported.¹⁶ The study was approved by the institutional review board or independent ethics committee at each centre and was conducted in accordance with Good Clinical Practice guidelines defined by the International Conference on Harmonisation. Nivolumab was provided by the sponsor (Bristol-Myers Squibb, Princeton, NJ, USA).

Eligibility criteria included: histologically confirmed squamous cell carcinoma of the oral cavity, pharynx, or larynx (including metastatic disease) that was not amenable to curative treatment and had progressed or recurred within 6 months of the last dose of platinum-based chemotherapy; aged ≥ 18 years; an Eastern Cooperative Oncology Group performance status score of 0 or 1; adequate bone marrow, hepatic, and renal function; and measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1.¹⁷ Key exclusion criteria included previous therapy targeting T-cell costimulating or immune-checkpoint pathways; known human immunodeficiency virus or hepatitis B or C virus infection; and active brain metastases, autoimmune disease, or systemic immunosuppression. After initial eligibility was established and informed consent had been obtained, patients were enrolled into the study via an interactive voice response system (IVRS). All patients provided written informed consent to participate based on the principles of the Declaration of Helsinki.

On 26 January 2016, the independent data monitoring committee reviewed the data at the planned interim analysis and declared OS superiority for nivolumab over IC therapy.¹⁶ The protocol was amended to allow patients in the IC arm to cross over to nivolumab. All patients not on active therapy are being followed for survival.

Randomisation and masking

Patients were randomly assigned 2:1 via IVRS to receive either nivolumab or IC. Randomisation was stratified by prior cetuximab use. The study was open-label; patients and investigators were not masked to treatment allocation.

Procedures

Patients received nivolumab 3 mg/kg as a 60-min intravenous infusion every 2 weeks, or IC therapy, consisting of weekly intravenous administrations of methotrexate (40–60 mg/m² of body surface area), docetaxel (30–40 mg/m²), or cetuximab (250 mg/m² after a loading dose of 400 mg/m²).

Disease assessments were done with computed tomography or magnetic resonance imaging at baseline, and every 6 weeks beginning at week 9. Imaging data were assessed by the investigators to establish tumour response according to RECIST version 1.1. Toxicity was assessed according to Common Terminology Criteria for Adverse Events v4.0 at each visit during the treatment phase and for 100 days after discontinuation. Patients remained on treatment until progression, intolerable toxicity, or withdrawal of consent. However, nivolumab treatment could be continued beyond disease progression, as assessed clinically or radiographically, if the investigator determined that it was providing clinical benefit. Patients were followed for OS every 3 months until death, loss to follow-up, or withdrawal of consent.

Formalin-fixed, paraffin-embedded tumour samples required for enrolment were centrally evaluated for tumour-cell membrane expression of programmed death ligand 1 (PD-L1) by immunohistochemistry (Dako North America) using a rabbit antihuman PD-L1 antibody (clone 28–8, Epitomics). Expression in a minimum of 100 evaluable tumour cells was scored for PD-L1 (1% or <1% expression).

Documentation of p16-positive or p16-negative disease to determine human papillomavirus status of tumour was required for patients with oropharyngeal cancer. Human papillomavirus p16 status was assessed by local or central laboratory immunohistochemical analysis. Samples were considered positive if >70% strong and diffuse nuclear and cytoplasmic staining specific to tumour cells was present.

The primary endpoint was OS and secondary endpoints were investigator-assessed progression-free survival and the rate of objective response per RECIST, version 1.1. PROs, including functioning, health status, and symptom burden, were included as exploratory endpoints. PRO assessments were at baseline prior to treatment initiation, at week 9, and then every 6 weeks during the treatment period using three validated patient-reported questionnaires^{8,9,18–22}: the 30-question cancer-specific European Organisation for the Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire–Core 30 (QLQ-C30); the 35-question head and neck cancer-specific EORTC Quality-of-Life Module for Head and Neck Cancer (QLQ-H&N35); and the three-level version of the European Quality of Life–5 Dimensions (EQ-5D-3L) questionnaire. Post-treatment assessments were made at follow-up visits 1 and 2 (35 ± 7 days and after the last treatment dose and 80 ± 7 days after follow-up visit 1). The EQ-5D-3L questionnaire was also administered at survival follow-up

visits (every 3 months $\pm$ 7 days after follow-up visit 2). Patients completed their assessments at each time point prior to physician contact, treatment dosing, or any procedures. PRO measures were self-administered by paper and pencil during the on-treatment phase and at follow-up visits 1 and 2. They were either self-administered by paper and pencil or completed via a telephone interview during survival follow-up. Specific information on reasons patients did not complete questionnaires were not collected, as this was not specified in the protocol.

The EORTC QLQ-C30 questionnaire (Version 3.0) consists of five functional scales (physical, role, social, emotional, and cognitive functioning), nine scales measuring symptoms or concerns relevant to cancer patients (fatigue, nausea and vomiting, pain, dyspnoea, insomnia, appetite loss, constipation, diarrhoea, and financial difficulties), as well as one scale measuring global health and QoL.^{23,24} For each functional and symptom question, patients responded to a 4-point categorical scale ranging from 1 (“not at all”) to 4 (“very much”); responses to the two items in the global health/QoL scale were given on a 7-point Likert scale. Item responses were aggregated and linearly transformed to a 0–100 scale according to the EORTC scoring manual.²⁵ From there, scales where higher scores represented higher symptom burden were reverse-scored to simplify presentation within this report so that for all scales a higher score represents better QoL.

The EORTC QLQ-H&N35 questionnaire consists of seven multi-item symptom scales (pain, sensory problems, social contact problems, swallowing, social eating problems, speech problems, and reduced sexuality) and 11 single-item symptom scales (nutritional supplement use, mouth opening problems, teeth problems, coughing, painkiller use, weight loss, weight gain, sticky saliva, feeding tube, dry mouth, and feeling ill).^{26,27} Most items were rated on a 4-point scale ranging from 1 (“not at all”) to 4 (“very much”); five components used a binary response set (“yes” or “no”). Patient responses were transformed to a 0–100 scale according to the EORTC scoring manual.²⁵ From there, scales were reverse-scored to simplify presentation within this report so that for all scales a higher score represents better QoL.

The EQ-5D-3L is a standardised questionnaire commonly used to measure self-reports of health status and functioning.^{28,29} It consists of two components, a descriptive system and visual analogue scale (VAS). The descriptive system covers five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), each of which is rated on a three-level scale (corresponding approximately to no, moderate, or extreme problems), resulting in a five-digit vector that describes a patient’s health state (eg, vectors 11111 and 33333 represent the best and worst health states possible, respectively). EQ-5D responses were weighted and aggregated using the United Kingdom preference-weighting algorithm³⁰ to produce utility scores measuring the value of a respondent’s health state to society, where a score of 0 was equivalent to being dead and 1 was equivalent to full health. The VAS is a vertical scale from 0 (worst imaginable) to 100 (best imaginable), on which patients were asked to report their overall health status on that day.

Outcomes

The primary endpoint of CheckMate 141 was OS, defined as time from randomisation to the date of death, reported previously.¹⁶ PRO analyses were exploratory endpoints. PRO

endpoints were interpreted based upon both statistically significant differences and clinically meaningful differences. Statistical differences in PRO endpoints included the evaluation of adjusted mean changes from baseline between treatment arms as assessed by the EORTC QLQ-C30, EORTC QLQ-H&N35, and EQ-5D-3L at each time point, and the time to clinically meaningful deterioration per each individual scale's criteria.

The clinically meaningful difference, indicating a change that would be detectable by patients and may mandate a change in the patient's management, was a score difference of 10 points for all domains on both EORTC questionnaires.³¹ Interpretation for the EORTC QLQ-C30 was also pre-specified based on newer subscale-specific guidelines, where clinically meaningful score differences vary by domain.^{32,33} A change from baseline of 10 points was also used as a clinically important deterioration within an individual for the time to deterioration analyses for all domains on both EORTC questionnaires. Score differences of 0.08 for the EQ-5D utility index and 7 for the EQ-5D VAS have been determined to be clinically relevant and were used as the clinically meaningful difference for these measures.

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Statistical analyses

The statistical analyses of the exploratory PRO endpoint were predefined in a PRO statistical analysis plan. Assessments were considered complete if at least half of the questions were completed/answered. Completion rates were calculated for each PRO measure as the proportion of patients alive in the study at the assessment time point with a completed questionnaire. In order to investigate the relationship of PRO scores with dropout, patients were grouped according to the timing of their last assessment and mean PRO scores plotted over time for each group by treatment arm. Patients with dropout after 21 weeks were combined because of small sample sizes.

QoL results within and between treatment arms were evaluated using descriptive statistics and analyses of covariance (ANCOVA), adjusted for the stratified randomisation (prior cetuximab therapy) and baseline score, at each time point when sample size was 10. The ANCOVA model treated change from baseline as the dependent variable and treatment and visit as fixed effects, with visits as a repeated measure. A separate analysis was performed for each domain, and only patients with questionnaires completed at baseline and at least one post-baseline assessment were included in the analysis. Missing data were not imputed.

P-values reported are for parametric tests with significance testing at the 0.05 level, with no adjustment for multiplicity. Interaction p-values are used to assess whether the treatment effect varied across the pre-specified subgroups (eg, baseline PD-L1 expression [$<1\%$ or 1%]).

The median time from randomisation to first deterioration (defined based on clinically meaningful change) was estimated by the Kaplan-Meier method, and two-sided 95% CI were computed using a generalisation of the Brookmeyer and Crowley method (log-log transformation). Deterioration was applied at the individual patient level; confirmation was not required at a subsequent visit; progression or death were not included as events or censored. A Cox proportional hazard regression model was used to estimate relative risk for

the time to deterioration, treating baseline score and prior cetuximab therapy as covariates. Hazard ratios were calculated for the risk of deterioration in the nivolumab arm over the IC arm, with ratios <1 representing decreased likelihood of experiencing deterioration in the nivolumab arm. All randomised patients were included in the time to deterioration analyses; these analyses include data collected at all available time points, including post-treatment follow-up. Patients with no baseline PRO data were censored to day 1; patients with baseline but no additional post-baseline data were censored to day 2.³⁴ This was necessary because Cox hazard ratio estimates can only be calculated on cases with non-missing baseline covariates.

Analyses were conducted using SAS (version 9.4, SAS Institute, Cary, NC, USA). This trial is registered with clinicaltrials.gov, number NCT02105636. The data cut-off point for the analyses of OS, progression-free survival, and safety was 18 December 2015 (planned interim analysis). Response and PRO data were based on a 5 May 2016 database lock.

Role of the funding source

The funders contributed to the study design, and the collection, analysis, and interpretation of the data in collaboration with the investigators and authors of this report. Funds for editorial and writing support were provided by the funder. All authors had full access to the raw data. The corresponding author had full access to all of the data and the final responsibility to submit for publication.

Results

Patients and population for analysis

A total of 361 patients were randomised to nivolumab (n=240) or IC (n=121). The median (interquartile range) follow-up for analysis was 4.6 (2.3–6.2) months. At baseline, 74–80% of patients completed PRO questionnaires (appendix p 3). However, completion rates decreased over time and diminishing sample size for the IC arm (n<10) precluded the performance of ANCOVA analyses of treatment-related differences beyond 15 weeks. Thus, 129 patients (nivolumab, n=93; IC, n=36) who completed any of the PRO questionnaires at baseline and at least one other assessment were included in change from baseline analyses. Baseline characteristics were similar between arms within this subset of patients (appendix p 4).

Mean graphs by the timing of last assessment showed that patients with only a baseline assessment (41.7–45.4% of the randomised sample) generally had lower functioning and higher symptoms compared with patients who provided PRO assessments at follow-up time points. EORTC QLQ-C30 and EORTC QLQ-H&N35 scores in the nivolumab arm were generally stable prior to dropout, whereas in the IC arm patients were either stable or declining prior to dropout. There were no clear trends in the EQ-5D data for either treatment arm prior to dropout.

Analysis of PROs using the EORTC QLQ-C30

Mean scores for all individual domains on the EORTC QLQ-C30 were similar between arms at baseline for the analytic cohort (n=127; appendix pp 5–6), with the exception of financial difficulties, and for the all-randomised population (see supplemental table S7 in Ferris, et al¹⁶). Treatment with nivolumab resulted in adjusted mean changes from baseline to weeks 9 and 15 ranging from –2.1 to +5.4 across functional and symptom domains measured by the EORTC QLQ-C30, indicating no clinically meaningful changes. In contrast, clinically meaningful deterioration occurred in 8 (53%) of the 15 domains in the IC arm at week 15 (decline of 10 points or more; appendix pp 5–6), with adjusted mean changes from baseline to weeks 9 and 15 ranging from –24.5 to +2.4. Examples shown in figure 1A are adjusted least squares mean changes from baseline for fatigue, dyspnoea, and appetite loss. Clinically meaningful improvement or deterioration by newer guidelines^{32,33} is indicated in appendix pp 5–6.

At both weeks 9 and 15, adjusted mean differences between arms were statistically significant and clinically meaningful (according to a difference of 10 points or greater) in favour of nivolumab for role functioning, social functioning, fatigue, dyspnoea, and appetite loss (figure 1B). Additional statistically significant and clinically meaningful differences favouring nivolumab were noted at either week 9 (diarrhoea) or week 15 (physical functioning, cognitive functioning, and insomnia). Further domains that were either statistically significant or clinically meaningful can be viewed in figure 1B. There were no statistically significant or clinically meaningful differences in favour of IC on the EORTC QLQ-C30.

In an exploratory analysis, we evaluated changes from baseline in EORTC QLQ-C30 scores among patients whose tumours had ≥1% or <1% PD-L1 expression (appendix p 7) or were p16-positive or p16-negative (appendix p 8). Adjusted mean differences between treatment arms were in line with the overall treatment effect for each domain, suggesting no evidence of a differential benefit across these subgroups.

Nivolumab significantly delayed the time to deterioration compared with IC for global health status; physical, role, cognitive, and social functioning; and symptoms of fatigue, dyspnoea, insomnia, and appetite loss on the EORTC QLQ-C30 (figure 2A, 2B and appendix p 9). Nivolumab treatment more than doubled the Kaplan-Meier estimate of the median time to first clinically meaningful deterioration compared with IC for physical and social functioning, pain, dyspnoea, and insomnia (figure 2B).

Analysis of PROs using the EORTC QLQ-H&N35

QoL outcomes as measured by the head and neck cancer-specific EORTC QLQ-H&N35 were consistent with the results of the EORTC QLQ-C30 analysis. At baseline, mean scores for individual domains were similar between arms for the analytic cohort (n=128; appendix pp 5–6), with the exceptions of social eating problems, teeth problems, dry mouth, and painkiller use, and for the all-randomised population (see supplemental table S7 in Ferris, et al¹⁶). Treatment with nivolumab resulted in adjusted mean changes from baseline to weeks 9 and 15 ranging from –4.1 to +15.3 across EORTC QLQ-H&N35 domains (figure 3A and

appendix pp 5–6). Changes from baseline in weight gain in the nivolumab arm were –13.2 at week 9 and –15.2 at week 15, indicating that patients experienced an increase in weight at these time points. In contrast, treatment with IC led to clinically meaningful deterioration (decline of 10 points or more) at week 15 for sensory problems, social eating problems, social contact problems, mouth opening problems, sticky saliva, feeling ill, painkiller use, and weight loss (appendix pp 5–6). The adjusted mean changes from baseline to weeks 9 and 15 for the IC arm ranged from –26.8 to +13.4.

At weeks 9 and 15, adjusted mean differences between arms were statistically significant and clinically meaningful (according to a difference of 10 points or greater) in favour of nivolumab for pain and sensory problems (figure 3B). Additional statistically significant and clinically meaningful differences favouring nivolumab were noted at either week 9 (nutritional supplement use) or week 15 (social contact problems, mouth opening problems, sticky saliva, feeling ill, painkiller use, and weight loss). Further domains that were either statistically significant or clinically meaningful can be viewed in figure 3B. Patients treated with nivolumab experienced more weight gain (difference not significant) and significantly less weight loss compared with IC. The trends observed for the change from baseline as measured by the EORTC QLQ-H&N35 were similar to the overall treatment effect regardless of PD-L1 expression (<1% or 1%; appendix p 10) or p16 status (appendix p 11) for each domain.

The median time to deterioration was significantly delayed by treatment with nivolumab compared with IC on the EORTC QLQ-H&N35 for pain, sensory problems, social contact problems, and mouth opening problems (appendix pp 12–14). Median time to clinically meaningful increase in weight was reached in the nivolumab arm, but not the IC arm.

Analysis of PROs using the EQ-5D-3L

The EQ-5D VAS, a measure of the patient's overall health status, was similar between arms at baseline for the analytic cohort (n=124; appendix pp 5–6) and all-randomised population (see supplemental table S7 in Ferris, et al¹⁶). However, patients in the nivolumab arm experienced a clinically meaningful improvement (according to a difference of 7 points or greater) in adjusted mean change in VAS score from baseline to week 15, in contrast to a clinically meaningful deterioration in the IC arm (appendix pp 5–6). Notably, the difference between arms at week 15 was both statistically significant and clinically meaningful in favour of nivolumab (figure 4A). The median time to deterioration on the EQ-5D VAS was not significantly different (figure 4B, 4C).

Baseline utility index score, a composite score representing the value placed by society on a respondent's current health state as defined based on the attributes measured by the EQ-5D, was similar in the two treatment arms (appendix pp 5–6). Neither statistically significant nor clinically meaningful differences in outcomes were observed at 9 or 15 weeks within or between arms (figure 4A). The median time to deterioration on the EQ-5D utility index was not statistically significant (figure 4B, 4C).

Discussion

Here we report that nivolumab stabilised several measures of QoL during the first 15 weeks of treatment of patients with platinum-refractory R/M SCCHN, and delayed time to deterioration compared with single-agent therapy of IC based on an exploratory analysis from CheckMate 141, a randomised, phase 3 trial. The clinical benefit, as measured by these validated PRO measures, indicates that patients experienced improved quality of life in addition to prolonged survival, higher response rate, and fewer high-grade toxicities relative to IC.¹⁶ These results are consistent with studies of nivolumab in melanoma, non-small cell lung cancer, and renal cell carcinoma, which demonstrated stable or improved QoL with nivolumab compared with dacarbazine, docetaxel, and everolimus, respectively.^{35–38}

Maximising the QoL of patients with cancer is increasingly recognised as an important therapeutic goal,^{1,10} particularly in the context of improved survival. Patients with SCCHN rank the ability to speak, swallow, and perform daily tasks in the absence of pain as very high priorities.^{39,40} Patients with R/M SCCHN face a dismal prognosis with poor QoL, including more severe social and psychological problems compared with patients with other cancers.¹ Both the disease and its treatments can have a significant impact on facial structures, causing anatomical and functional defects. Patients with R/M SCCHN may have residual toxicities caused by prior systemic therapies that can impact performance status, limit the administration of subsequent treatments, and predispose patients to developing additional toxicities.¹⁰

The results presented here interpret a larger positive difference in change (nivolumab minus IC) as better, for all domains. This confounds the interpretation of changes in weight, as all symptom domains, including weight gain and weight loss, were scored in the same direction. At week 15, our results showed a positive difference for weight loss (interpreted as favoring nivolumab) but a negative difference for weight gain (interpreted as favoring IC) as a result of scoring algorithms applied to the weight loss and weight gain domains. In fact, nivolumab was associated with less weight loss and more weight gain than IC. Given that 35–50% of patients with SCCHN experience weight loss⁴¹ and often have difficulties eating, weight gain can be viewed as a positive effect in this population. Taken together, results for weight loss and weight gain suggest that, at 15 weeks, patients treated with nivolumab exhibited a more desirable trajectory in weight than did those treated with IC.

In our analyses, the endpoint predefined in the statistical analysis plan was “time to QoL deterioration,” which does not include death as an event. There is no consensus on the best definition to use for time to deterioration analyses; however, our analysis followed current recommendations.³⁴ Importantly, the threshold used to determine clinical relevance on the EORTC QLQ-C30 (10 points) is based on observations in other cancers. Based on a recent meta-analysis from Cocks et al, consisting of multiple cancers and a variety of clinical situations, clinically meaningful differences may in fact be seen at even lower thresholds.^{32,33} Therefore, the use of a 10-point difference in our manuscript is likely a conservative estimate of within and between-treatment arm differences. With the newer guidelines, additional domains demonstrated improvement with nivolumab or deterioration with IC, indicating that the overall clinical benefit of nivolumab may be even greater.

To our knowledge, this is the first comprehensive report on PROs for an immunotherapy agent in SCCHN. Furthermore, few studies have reported on the QoL, symptom burden, or functioning in patients with R/M SCCHN.^{1,7,10} In the EXTREME study, where patients received platinum-fluorouracil alone or in combination with cetuximab as first-line therapy for R/M SCCHN, a limited number of domains on the EORTC QLQ-C30 and EORTC QLQ-H&N35 were reported.⁸ The results showed that at cycle 3 and month 6, QoL was not significantly worse with the addition of cetuximab. At cycle 3, pain, swallowing, speech problems, and social eating problems significantly favoured the cetuximab arm on the QLQ-H&N35, whereas improvements on the QLQ-C30 were not significant after adjusting for baseline score. In the platinum-refractory setting, a study of afatinib vs methotrexate showed an improvement in pain on the EORTC QLQ-H&N35 with afatinib vs methotrexate, but no differences in swallowing or global health status.⁹ The median time to deterioration was statistically longer with afatinib for these measures, but medians ranged from 2.1 to 2.7 months for methotrexate and from 3.0 to 3.8 months for afatinib. Whereas previous trials have shown limited QoL impacts on only a few outcomes, results presented here demonstrate consistency across several questionnaires and a large number of relevant outcomes. Patients benefitted from nivolumab regardless of both PD-L1 and p16 status.

Although the questionnaires used in this trial have been used previously in numerous clinical trials, their validation has been conducted primarily in patients with locally advanced disease¹⁰; thus, it is possible that certain symptoms of importance in R/M SCCHN could have been missed in this and other trials. Furthermore, the EQ-5D is a measure that can be used in general or targeted clinical populations, and is not apt to be as sensitive as a condition-targeted measure that is used in the designated population. However, the EQ-5D includes other measures that are important to patients with SCCHN such as anxiety/depression, as well as measures not covered by the EORTC measures such as the ability to do general, daily activities.

No adjustment for multiple testing for exploratory endpoints is a common and widely accepted statistical practice. However, this could also be a limitation of the study in that a lack of alpha hierarchy and failing to adjust for multiplicity could have some implications for inferences that are close to the 0.05 benchmark. As is common with PROs,^{8,10,19} our analysis was also limited by relatively low completion rates. After week 15, numbers in the IC arm were so few as to preclude statistical comparisons between arms. Questionnaire response rates typically correspond to patient morbidity and functional status; patients affected by physical and psychological factors such as fatigue and depression may be unable to complete the assessments, depending on the response format, delivery, and length of the questionnaire.^{1,7,42} One possible explanation for the higher level of missing data in the IC arm is the potential bias of an open-label study, where the patient's excitement about the investigational agent may lead to more enthusiastic participation, including completion of questionnaires or ranking the agent positively. To explore the impact of patients being aware of their treatment allocation, baseline QoL scores were compared across arms to determine if there was a consistent bias. Across the 15 EORTC QLQ-C30 domains and 18 EORTC QLQ-H&N35 domains, only five domains had differences across the arms, worse financial difficulties, social eating, teeth problems, and dry mouth in the IC arm, and higher painkiller use in the nivolumab arm. Some of these differences may be expected by chance across this

number of domains, and this does not seem to imply a consistent bias in the QoL responses towards the nivolumab arm. Baseline scores were accounted for in the ANCOVA analyses. This also may have been affected by differential progression or the higher number of patients experiencing prolonged disease control in the nivolumab arm, whereby patients may have maintained the ability to respond to their questionnaires, as well as maintaining their QoL. Another possible explanation is the known acute toxicity associated with therapies used in the IC arm. Similar attrition has been observed in prior studies in patients with SCCHN, with those discontinuing generally representing patients with the worst QoL,^{8,20,43} and presenting a significant challenge for statistical analyses. For example, during the EXTREME trial, only 44% of patients had both an evaluable baseline and a post-baseline assessment.⁸ The nature of the missing data was investigated in order to understand the impact on results presented. The analysis population was similar to the full study population in terms of most demographics and disease characteristics. Generally, patients with only a baseline assessment had lower functioning and worse symptom scores compared with those providing further QoL assessments. Prior to dropout, EORTC domain scores were stable in the nivolumab arm but declined in the IC arm. This would suggest that our estimates of treatment differences are likely to be conservative.

The results of CheckMate 141 suggest that nivolumab is the first PD-1 inhibitor to our knowledge to demonstrate a significant improvement in OS, with better tolerability and a QoL benefit, compared with standard therapy for platinum-refractory R/M SCCHN. Given the significant unmet need in this population and the importance of maintaining or improving QoL for patients with R/M SCCHN, these data support nivolumab as a new standard of care option in this setting.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Declaration of interests

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Research in context

Evidence before this study

We searched prospective clinical trial publications indexed in PubMed during the past 10 years (1 December 2006 to 1 December 2016) for the title or abstract terms “head and neck” and “carcinoma” or “cancer” and “quality of life” and “recurrent” or “metastatic”. The search returned 15 publications, most of which used chemotherapy-based combinations. Among platinum-refractory patients, no treatment was noted as having significant improvements on quality of life (QoL). The search returned only one report on QoL in a trial investigating the use of a checkpoint inhibitor for squamous cell carcinoma of the head and neck (SCCHN): the phase 3 CheckMate 141 study, which compared nivolumab with single-agent therapy of investigator’s choice (IC) in patients with recurrent or metastatic (R/M) SCCHN. In CheckMate 141, overall survival was significantly longer for patients treated with nivolumab than for those treated with IC. Grade 3 or 4 treatment-related adverse events were less frequent with nivolumab *vs* IC. The study reported that mean changes from baseline in patient-reported outcome (PRO) domains assessed on the European Organisation for the Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire–Core 30 (QLQ-C30) and the EORTC head and neck cancer–specific module (EORTC QLQ-H&N35) were stable for patients treated with nivolumab and deteriorated for patients treated with IC.

Added value of this study

Our study provides complete CheckMate 141 patient-reported QoL analyses for the overall population and subgroups of clinical interest. To our knowledge, this is the first study demonstrating PROs from a clinical trial evaluating a checkpoint inhibitor antibody in patients with R/M SCCHN. Nivolumab-treated patients maintained baseline levels of QoL, as assessed by three validated PRO measures. In contrast, IC led to clinically meaningful deteriorations. Nivolumab treatment led to a statistically significant delay in deterioration across a number of QoL domains compared with IC.

Implications of all the available evidence

Combined with the primary report from CheckMate 141, results from this study indicate that treatment with nivolumab offers a new therapeutic approach to extend survival that may also preserve or enhance QoL in patients with advanced SCCHN.

Figure 1: EORTC QLQ-C30 ANCOVA analyses
Adjusted mean change from baseline in fatigue, dyspnoea, and appetite loss at weeks 9 and 15 (A) and LS mean difference between treatment arms (B). Dashed lines indicate clinically meaningful change (10 points). The number of evaluable patients for each time point, domain, and treatment arm can be found in the appendix, page 5. ANCOVA = analysis of covariance. CI=confidence interval. EORTC QLQ-C30=European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire–Core 30. IC=investigator’s choice. LS=least squares. Nivo=nivolumab.

Figure 2: Time to deterioration (Kaplan-Meier plots of time to first clinically meaningful deterioration, A) and Kaplan-Meier estimate of median time to deterioration and HR (95% CI) for the EORTC QLQ-C30 (B) among all randomised patients

The number of evaluable patients for each time point, domain, and treatment arm in A can be found in the appendix, page 5. CI=confidence interval. EORTC QLQ-C30=European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire–Core 30. HR=hazard ratio. IC=investigator’s choice. NE=not estimable. Nivo=nivolumab. TTD=time to deterioration.

Figure 3: EORTC QLQ-H&N35 ANCOVA

Adjusted mean (95% CI) change from baseline in mouth opening problems, sticky saliva, and feeling ill at weeks 9 and 15 (A) and adjusted least squares (LS) mean difference between treatment arms (B). Dashed lines indicate clinically meaningful change (10 points). The number of evaluable patients for each time point, domain, and treatment arm can be found in the appendix, page 5. ANCOVA=analysis of covariance. CI=confidence interval. EORTC QLQ-H&N35=European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire head and neck cancer-specific module. IC= investigator's choice. Nivo=nivolumab. *A negative value indicates an increase in weight gain.

Figure 4: EQ-5D-3L: Adjusted LS mean difference (95% CI) between nivolumab and investigator's choice at weeks 9 and 15 (A); and time to deterioration (Kaplan-Meier plot of time to first clinically meaningful deterioration [B]) and Kaplan-Meier estimate of median time to deterioration and HR (95% CI) (C)

Dashed lines in A indicate clinically meaningful change (0.08 and 7 points for the utility index and VAS, respectively). CI=confidence interval. EQ-5D-3L=three-level European Quality of Life–5 Dimensions questionnaire. HR=hazard ratio. IC=investigator's choice. LS=least squares. Nivo=nivolumab. VAS=visual analogue scale. TTD=time to deterioration.