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

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Summary

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

Methods CheckMate 141 was a randomised, open-label, phase 3 trial in patients with recurrent or metastatic squamous cell carcinoma of the head and neck who progressed within 6 months after platinum-based chemotherapy. Patients were randomly assigned (2:1) to nivolumab 3 mg/kg every 2 weeks (n=240) or investigator's choice (n=121) of methotrexate (40–60 mg/m^2 of body surface area), docetaxel (30–40 mg/m^2), or cetuximab (250 mg/m^2 after a loading dose of 400 mg/m^2) until disease progression, intolerable toxicity, or withdrawal of consent. On Jan 26, 2016, the independent data monitoring committee reviewed the data at the planned interim analysis and declared overall survival superiority for nivolumab over investigator's choice therapy (primary endpoint; described previously). The protocol was amended to allow patients in the investigator's choice group 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 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 groups in PROs were analysed by ANCOVA among patients with baseline and at least one other assessment. All randomised patients were included in the time to clinically meaningful deterioration analyses. Median time to clinically meaningful deterioration was analysed by

Kaplan-Meier methods. CheckMate 141 was registered with ClinicalTrials.org, number NCT02105636.

Findings Patients were enrolled between May 29, 2014, and July 31, 2015, and subsequently 361 patients were randomly assigned to receive nivolumab (n=240) or investigator's choice (n=121). Among them, 129 patients (93 in the nivolumab group and 36 in the investigator's choice group) completed any of the PRO questionnaires at baseline and at least one other assessment. 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. By contrast, eight (53%) of the 15 domains in the investigator's choice group showed 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 no domains in the nivolumab group and eight (44%) of 18 domains in the investigator's choice group. Patients in the nivolumab group had 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 investigator's choice group (7·3 *vs* −7·8). Differences between groups were 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 versus investigator's choice 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 investigator's choice led to clinically meaningful deterioration. Nivolumab delayed time to deterioration of patient-reported quality-of-

life outcomes compared with single-agent therapy of investigator's choice in patients with platinum-refractory recurrent or metastatic squamous cell carcinoma of the head and neck. In view of the major unmet need in this population and the importance of maintaining or improving quality of life for patients with recurrent or metastatic squamous cell carcinoma of the head and neck, these data support nivolumab as a new standard-of-care option in this setting.

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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 (Dec 1, 2006, to Dec 1, 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. The search returned only one report on quality of life in a trial investigating the use of a checkpoint inhibitor for squamous cell carcinoma of the head and neck: the phase 3 CheckMate 141 study, which compared nivolumab with single-agent therapy of investigator's choice in patients with recurrent or metastatic squamous cell carcinoma of the head and neck. In CheckMate 141, overall survival was significantly longer for patients treated with nivolumab than for those treated with investigator's choice. Grade 3 or 4 treatment-related adverse events were less frequent with nivolumab versus investigator's choice. The study reported that mean changes from baseline in patient-reported outcome (PRO) domains assessed on the European Organisation for 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 investigator's choice.

Added value of this study

Our study provides complete CheckMate 141 patient-reported quality of life analyses for the overall population and subgroups of clinical interest. To our knowledge, this is the first study showing PROs from a clinical trial assessing a checkpoint inhibitor antibody in patients with recurrent or metastatic squamous cell carcinoma of the head and neck. Patients treated with nivolumab maintained baseline levels of quality of life, as assessed by three validated PRO measures. By contrast, investigator's choice led to clinically meaningful deteriorations. Nivolumab treatment led to a significant delay in deterioration across a number of quality of life domains compared with investigator's choice.

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 might also preserve or enhance quality of life in patients with advanced squamous cell carcinoma of the head and neck.

Introduction

Squamous cell carcinoma of the head and neck, including cancers of the oral cavity, pharynx, and larynx, and its treatment have a major effect on patient quality of life.[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, chemoradiotherapy, or both.[2] Consequently, changes to basic physical functions, physical appearance, and social interactions are common among patients with squamous cell carcinoma of the head and neck.[3] Patients with squamous cell carcinoma of the head and neck have been shown to bear greater psychological distress than those patients 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 quality of life, patients with recurrent or metastatic squamous cell carcinoma of the head and neck have a dismal prognosis. Median overall survival 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 quality of life in a small number of clinical trials of chemotherapy and targeted therapies in recurrent or metastatic squamous cell carcinoma of the head and neck, few of which have shown improvements or significant differences between treatment groups.[7–10] However, baseline quality of life scores have been reported to be independent prognostic factors for overall survival in patients with recurrent or metastatic head and neck cancer.[11] Therefore, there is a large unmet medical need for treatments that improve prognosis as well as preserve and maximise quality of life.

Because squamous cell carcinoma of the head and neck 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 squamous cell carcinoma of the head and neck.[12–16]

In CheckMate 141, nivolumab showed improved overall survival compared with single-agent therapy of investigator's choice in patients with recurrent or metastatic squamous cell carcinoma of the head and neck.[16] Median overall survival was 7·5 months (95% CI 5·5–9·1) with nivolumab and 5·1 months (4·0–6·0) with investigator's choice (HR 0·70 [97·73% CI 0·51–0·96]; p=0·01). Estimated 1-year survival was more than doubled with nivolumab compared with investigator's choice (36·0% [95% CI 28·5–43·4] *vs* 16·6% [8·6–26·8]). Grade 3 or 4 treatment-related adverse events occurred in 13% of patients treated with nivolumab compared with 35% of those treated with investigator's choice. Moreover, a preliminary analysis of PROs showed that nivolumab stabilised quality of life, by contrast with clinically meaningful deterioration observed in patients treated with investigator's choice. Here, we report the full quality-of-life 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 recurrent or metastatic squamous cell carcinoma of the head and neck compared with single-agent therapy of investigator's choice. Patients were randomly assigned to treatment 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]

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 or older; 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 HIV or hepatitis B or C virus infection; and active brain metastases, auto-immune 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. All patients provided written informed consent to participate based on the principles of the Declaration of Helsinki. The study was approved by the institutional review board or independent ethics committee at each centre and was done 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).

On Jan 26, 2016, the independent data monitoring committee reviewed the data at the planned interim analysis and declared overall survival superiority for nivolumab over investigator's choice therapy.[16] The protocol was amended to allow patients in the investigator's choice group 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 an interactive voice response system to receive either nivolumab or investigator's choice. Randomisation was stratified by previous 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 investigator's choice 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) until disease 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.

Disease assessments were done with CT or MRI 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 version 4.0 at each visit during the treatment phase and for 100 days after discontinuation. Patients were followed for overall survival every 3 months until death, loss to follow-up, or withdrawal of consent.

Formalin-fixed, paraffin-embedded tumour samples required for enrolment were centrally assessed for tumour-cell membrane expression of programmed death ligand 1 (PD-L1) by immunohistochemistry (Dako North America, Carpinteria, CA, USA) using a rabbit antihuman PD-L1 antibody (clone 28–8, Epitomics, Burlingame, CA, USA). 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 (HPV) status of tumour was required for patients with oropharyngeal cancer. HPV p16 status was assessed by local or central laboratory immunohistochemical analysis. Samples were considered positive if more than 70% strong and diffuse nuclear and cytoplasmic staining specific to tumour cells was present.

PRO assessments were done at baseline before 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 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 days give or take 7 days after the last treatment dose, and 80 days give or take 7 days after follow-up visit 1). The EQ-5D-3L questionnaire was also administered at survival follow-up visits (every 3 months give or take 7 days after follow-up visit 2). Patients completed their assessments at each timepoint before 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 about reasons patients did not complete questionnaires were not collected, because 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 patients with cancer (fatigue, nausea and vomiting, pain, dyspnoea, insomnia, appetite loss, constipation, diarrhoea, and financial difficulties), as well as one scale measuring global health and quality of life.[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 and quality-of-life 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 quality of life.

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 quality of life.

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 a visual analogue scale (VAS). The descriptive system covers five dimensions (mobility, self-care, usual activities, pain or discomfort, and anxiety or depression), each of which is rated on a three-level scale (corresponding roughly to no problems, moderate problems, 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 UK preference-weighting algorithm[30] 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 overall survival, defined as time from randomisation to the date of death, reported previously.[16] Secondary endpoints were investigator-assessed progression-free survival and the proportion of participants who achieved

an objective response per RECIST version 1.1. PRO analyses were exploratory endpoints. PRO endpoints were interpreted based upon both significant differences and clinically meaningful differences. Statistical differences in PRO endpoints included evaluation of adjusted mean changes from baseline between treatment groups as assessed by the EORTC QLQ-C30, EORTC QLQ-H&N35, and EQ-5D-3L at each timepoint, 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 might mandate a change in the patient's management, was a score difference of 10 points or more for all domains on both EORTC questionnaires.[31] Interpretation for the EORTC QLQ-C30 was also prespecified 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 or more for the EQ-5D utility index and 7 or more for the EQ-5D VAS have been determined to be clinically relevant and were used as the clinically meaningful difference for these measures.[22]

Statistical analyses

The statistical analysis 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 or answered. Completion rates were calculated for each PRO measure as the proportion of patients alive in the study at the assessment timepoint with a completed questionnaire. To investigate the relation 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 group. Patients with dropout after 21 weeks were combined because of small sample sizes.

Quality of life results within and between treatment groups were assessed using descriptive statistics and ANCOVA, adjusted for the stratified randomisation (previous cetuximab therapy) and baseline score, at each timepoint when sample size was 10 or more. 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 done 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 prespecified subgroups (eg, baseline PD-L1 expression [<1% or ≥1%]).

Median time from randomisation to first deterioration (defined based on clinically meaningful change) was estimated by the Kaplan-Meier method, and two-sided 95% CIs 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 previous cetuximab therapy as covariates. Hazard ratios (HRs) were calculated for the risk of deterioration in the nivolumab group over the investigator's choice group, with ratios less than 1 representing decreased likelihood of experiencing deterioration in the nivolumab group. All randomised patients were included in the time-to-deterioration analyses; these analyses include data collected at all available timepoints, 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 censoring was necessary because Cox hazard ratio estimates can only be calculated on cases with non-missing baseline covariates.

The data cutoff point for the analyses of overall survival, progression-free survival, and safety was Dec 18, 2015 (planned interim analysis). Response and PRO data were based on a May 5, 2016, database lock.

Data were analysed with SAS (version 9.4, SAS Institute, Cary, NC, USA).

This trial is registered with ClinicalTrials.gov, number NCT02105636.

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

Between May 29, 2014, and July 31, 2015, patients were enrolled, and subsequently 361 patients were randomly assigned to receive nivolumab (n=240) or investigator's choice (n=121). Median follow-up for analysis was 4·6 months (IQR 2·3–6·2). At baseline, 74–80% of patients completed PRO questionnaires (appendix p 3). However, completion rates decreased over time and diminishing sample size for the investigator's choice group (n<10) precluded the performance of ANCOVA analyses of treatment-related differences beyond 15 weeks. Thus, 129 patients (93 in the nivolumab group and 36 in the investigator's choice group) 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 treatment groups 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 timepoints. EORTC QLQ-C30 and EORTC QLQ-H&N35 scores in the nivolumab group were generally stable before dropout, whereas in the investigator's choice group, patients were either stable or declining before dropout. No clear trends in the EQ-5D data were noted for either treatment group before dropout (data not shown).

Mean scores for all individual domains on the EORTC QLQ-C30 were similar between groups at baseline for the analytical cohort (n=127; 91 in the nivolumab group and 36 in the investigator's choice group; appendix pp 5, 6), with the exception of financial difficulties (nivolumab, 18·9 [SD 24·5]; investigator's choice, 31·5 [36·5]; appendix pp 5, 6), and for the all-randomised population (see supplementary table 7 in Ferris et al[16]). 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. By contrast, clinically meaningful deterioration occurred in eight (53%) of the 15 domains in the investigator's choice group 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 the appendix (pp 5, 6).

At both weeks 9 and 15, adjusted mean differences between groups were 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 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 significant or clinically meaningful are shown in figure 1B. No

significant or clinically meaningful differences were noted in favour of investigator's choice on the EORTC QLQ-C30.

In exploratory analyses, we assessed changes from baseline in EORTC QLQ-C30 scores among patients whose tumours had 1% or more or less than 1% PD-L1 expression (appendix p 7) or were p16-positive or p16-negative (appendix p 8). Adjusted mean differences between treatment groups 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 investigator's choice 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 2; appendix p 9). Nivolumab treatment more than doubled the Kaplan-Meier estimate of the median time to first clinically meaningful deterioration compared with investigator's choice for physical and social functioning, pain, dyspnoea, and insomnia (figure 2B).

Quality-of-life 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 groups for the analytical 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 supplementary table 7 in Ferris et al[16]). 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; appendix pp 5, 6). Changes from baseline in weight gain in the nivolumab group were −13·2 at week 9 and −15·2 at week 15, indicating that patients experienced an increase in weight at these timepoints. By contrast, treatment with investigator's choice 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 investigator's choice group ranged from −26·8 to 13·4.

At weeks 9 and 15, adjusted mean differences between groups were 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 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 significant or clinically meaningful are shown in figure 3B. Patients treated with nivolumab experienced more weight gain (difference not significant) and significantly less weight loss compared with investigator's choice. 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.

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

The EQ-5D VAS, a measure of the patient's overall health status, was similar between groups at baseline for the analytical cohort (n=124; appendix pp 5, 6) and all-randomised population (see supplementary table 7 in Ferris et al[16]). However, patients in the nivolumab group had 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, by contrast with a clinically meaningful deterioration in the investigator's choice group (7·3 *vs* –7·8; appendix pp 5, 6). Notably, the difference between groups at week 15 was both significant and clinically

meaningful in favour of nivolumab (figure 4A). 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 groups (appendix pp 5, 6). Neither significant nor clinically meaningful differences in outcomes were observed at 9 or 15 weeks within or between groups (figure 4A). Median time to deterioration on the EQ-5D utility index was not significant (figure 4B, 4C). Median time to deterioration was significantly longer with nivolumab versus investigator's choice for 13 (37%) of 35 domains assessed across the three questionnaires.

Discussion

Here we report that nivolumab stabilised several measures of quality of life during the first 15 weeks of treatment of patients with platinum-refractory recurrent or metastatic squamous cell carcinoma of the head and neck, and delayed time to deterioration compared with single-agent therapy of investigator's choice 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 investigator's choice.[16] These results are consistent with studies of nivolumab in melanoma, non-small-cell lung cancer, and renal cell carcinoma, which showed stable or improved quality of life with nivolumab compared with dacarbazine, docetaxel, and everolimus, respectively.[35–38]

Maximising the quality of life of patients with cancer is increasingly recognised as an important therapeutic goal,[1,10] particularly in the context of improved survival. Patients with squamous cell carcinoma of the head and neck rank the ability to speak, swallow, and perform daily tasks in the absence of pain as very high priorities.[39,40] Patients with recurrent or

metastatic squamous cell carcinoma of the head and neck face a dismal prognosis with poor quality of life, including more severe social and psychological problems than those with other cancers.[1] Both the disease and its treatments can have a major effect on facial structures, causing anatomical and functional defects. Patients with recurrent or metastatic squamous cell carcinoma of the head and neck might have residual toxicities caused by previous systemic therapies that can affect performance status, restrict 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 investigator's choice) as better, for all domains. This confounds the interpretation of changes in weight, because 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 favouring nivolumab) but a negative difference for weight gain (interpreted as favouring investigator's choice) 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 investigator's choice. In view that 35–50% of patients with squamous cell carcinoma of the head and neck experience weight loss[41] and often have difficulties eating, weight gain can be viewed as a positive effect in this population. 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 investigator's choice.

In our analyses, the endpoint predefined in the statistical analysis plan was time to quality-of-life deterioration, which does not include death as an event. No consensus exists 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 and colleagues[32,33] consisting of multiple cancers and a variety of clinical situations, clinically meaningful differences might in fact be seen at even lower

thresholds. Therefore, the use of a 10-point difference in our manuscript is probably a conservative estimate of within and between-treatment group differences. With the newer guidelines, additional domains showed improvement with nivolumab or deterioration with investigator's choice, indicating that the overall clinical benefit of nivolumab might be even greater.

To our knowledge, this is the first comprehensive report on PROs for an immunotherapy agent in squamous cell carcinoma of the head and neck. Furthermore, few studies have reported on the quality of life, symptom burden, or functioning in patients with recurrent or metastatic squamous cell carcinoma of the head and neck.[1,7,10] In the EXTREME study,[8] where patients received platinum-fluorouracil alone or in combination with cetuximab as first-line therapy for recurrent or metastatic squamous cell carcinoma of the head and neck, few domains on the EORTC QLQ-C30 and EORTC QLQ-H&N35 were reported. The results showed that at cycle 3 and month 6, quality of life was not significantly worse with the addition of cetuximab. At cycle 3, pain, swallowing, speech problems, and social eating problems significantly favoured the cetuximab group on the QLQ-H&N35, whereas improvements on the QLQ-C30 were not significant after adjustment for baseline score. In the platinum-refractory setting, a study of afatinib versus methotrexate showed an improvement in pain on the EORTC QLQ-H&N35 with afatinib versus methotrexate, but no differences in swallowing or global health status.[9] Median time to deterioration was statistically longer with afatinib for these measures, but medians ranged from 2·1 months to 2·7 months for methotrexate and from 3·0 months to 3·8 months for afatinib. Whereas previous trials have shown limited quality-of-life effects on only a few outcomes, results presented here show 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 several clinical trials, their validation has been done primarily in patients with locally advanced

disease;[10] thus, it is possible that certain symptoms of importance in recurrent or metastatic squamous cell carcinoma of the head and neck 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 squamous cell carcinoma of the head and neck such as anxiety and 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 an absence 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 investigator's choice group were so few as to preclude statistical comparisons between groups. Questionnaire response rates typically correspond to patient morbidity and functional status; patients affected by physical and psychological factors such as fatigue and depression might 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 investigator's choice group is the potential bias of an open-label study, where the patient's excitement about the investigational agent might lead to more enthusiastic participation, including completion of questionnaires or ranking the agent positively. To explore the effect of patients being aware of their treatment allocation, baseline quality-of-life scores were compared across groups to determine whether 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 groups—worse financial difficulties, social eating, teeth problems, and dry mouth in the investigator's choice group, and increased painkiller use in the nivolumab group. Some of these

differences might be expected by chance across this large number of domains, and this does not seem to imply a consistent bias in the quality-of-life responses towards the nivolumab group. Baseline scores were accounted for in the ANCOVA analyses. This might also have been affected by differential progression or the higher number of patients experiencing prolonged disease control in the nivolumab group, whereby patients could have maintained the ability to respond to their questionnaires, as well as maintaining their quality of life. Another possible explanation is the known acute toxicity associated with therapies used in the investigator's choice group. Similar attrition has been noted in previous studies in patients with squamous cell carcinoma of the head and neck, with those discontinuing generally representing patients with the worst quality of life,[8,20,43] and presenting a significant challenge for statistical analyses. For example, during the EXTREME trial,[8] only 44% of patients had both an evaluable baseline and a post-baseline assessment. The nature of the missing data was investigated to understand the effect 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 than those providing further quality-of-life assessments. Before dropout, EORTC domain scores were stable in the nivolumab group but declined in the investigator's choice group. 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 show a significant improvement in overall survival, with better tolerability and a quality-of-life benefit, compared with standard therapy for platinum-refractory recurrent or metastatic squamous cell carcinoma of the head and neck. In view of the major unmet need in this population and the importance of maintaining or improving quality of life for patients with recurrent or metastatic squamous cell carcinoma of the head and neck, these data support nivolumab as a new standard of care option in this setting.

Contributors

JWS, MM, ML, FT, MD, LM, KC, and MLG contributed to the conception and design of the study and statistical analysis plan. KJH, RLF, GB, ADC, JF, LL, SK, CE, EEV, FW, NFS, NK, RH, MT, VG, MLG, and JG treated patients and collected data. JWS, FT, MD, KC, and LM assembled the data and did the statistical analyses. All authors contributed to the data analysis and interpretation. All authors had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors contributed to the drafting of the manuscript or critical revision of the manuscript for important intellectual content. All authors provided final approval of the manuscript. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Declaration of interests

KJH reports consultancy from AstraZeneca, Bristol-Myers Squibb, Merck, Merck Sharp & Dohme, and Pfizer. RLF reports advisory board participation from Amgen, AstraZeneca/MedImmune, Bristol-Myers Squibb, Merck, and Pfizer; research funding from AstraZeneca/ MedImmune, Bristol-Myers Squibb, Merck, and VentiRx. GB reports consultancy from AbbVie, Ariad, AstraZeneca, Bayer, Bristol-Myers Squibb, Celgene, Clovis, and Merck; research funds from AbbVie, AstraZeneca, Bayer, Bristol-Myers Squibb, Celgene, Genentech, GlaxoSmithKline, Merck, Novartis, and Xcovery. JF reports personal fees from AstraZeneca and Bristol-Myers Squibb. LL reports a consultancy and advisory role for Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Debiopharm, Eisai, Merck Serono, Merck Sharp & Dohme, Novartis, Sobi, and Roche; research funding from AstraZeneca, Boehringer Ingelheim, Eisai, Merck Serono, Merck Sharp & Dohme, Novartis, and Roche; and travel expenses for medical meetings from Amgen, Bayer, Debiopharm, Merck Serono, and Sobi. SK reports personal fees for advisory board participation from Bristol-Myers Squibb and Merck

Sharp & Dohme. CE reports personal fees from Bristol-Myers Squibb, Innate Pharma, Merck Sharp & Dohme, and Merck Serono. EEV reports consultant role for Bristol-Myers Squibb. FW reports advisory board participation for Merck; and clinical trial funding from AstraZeneca, Bayer, Bristol-Myers Squibb, and Merck. NFS reports consultancy fees from Bristol-Myers Squibb, Lilly, Merck, and Pfizer. NK reports grants for research funding from AstraZeneca; Eisai, Nippon Boehringer Ingelheim, and ONO Pharmaceutical; personal fees for honoraria from Eisai and ONO Pharmaceutical; and personal fees for seminar presentation from AstraZeneca, Bristol-Myers Squibb, Eisai, and Merck Serono. RH reports grants, personal fees, and non-financial support from Bristol-Myers Squibb; grants and personal fees from AstraZeneca, Celgene, Merck, and Pfizer. MT reports grants and personal fees for advisory boards and lecture honoraria from Bristol-Myers Squibb; personal fees for advisory boards and lecture honoraria from Bayer; personal fees for advisory boards and research funding from Merck Sharp & Dohme; grants for research funding and personal fees for advisory boards from AstraZeneca, ONO Pharmaceutical, and Pfizer; grants for research funding and personal fees for lecture honoraria from Eisai; personal fees for lecture honoraria from Otsuka; and grants for research funding from Boehringer Ingelheim, NanoCarrier, and Novartis. VG reports personal fees from AstraZeneca, Bristol-Myers Squibb, Merck Sharp & Dohme, and Merck Serono; and grants from Pfizer (Wyeth). JWS reports employment and stocks from Bristol-Myers Squibb. MM reports employment by Bristol-Myers Squibb. ML reports employment by Bristol-Myers Squibb. FT reports employment by Adelphi Values, the entity paid for patient-reported outcome analyses in this manuscript. MD reports employment by Adelphi Values, the entity paid for patient-reported outcome analyses in this manuscript. LM reports employment by Adelphi Values, the entity paid for patient-reported outcome analyses in this manuscript. KC reports employment by Adelphi Values, the entity paid for patient-reported outcome analyses in this manuscript; personal fees from Amgen, AstraZeneca, Celgene, EndoMag, and Onyx Pharmaceuticals. MLG reports honoraria from Amgen, AstraZeneca, Bristol-Myers Squibb, Celgene, GlaxoSmithKline,

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FIGURES

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 least square (LS) mean difference between treatment groups (B). Dashed lines indicate clinically meaningful change (10 points). The number of evaluable patients for each timepoint, domain, and treatment group can be found in the appendix (p 5). EORTC QLQ-C30=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30.

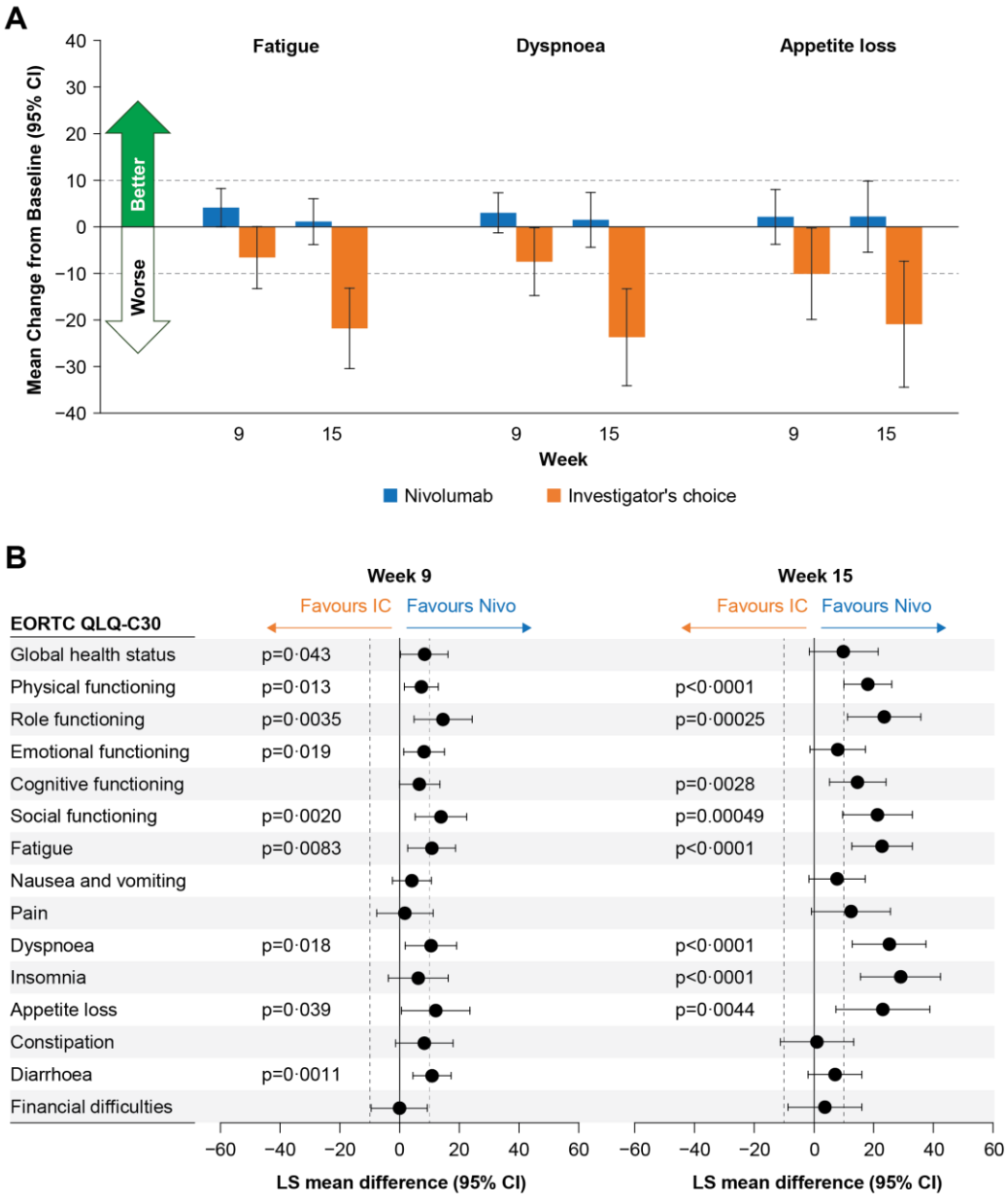
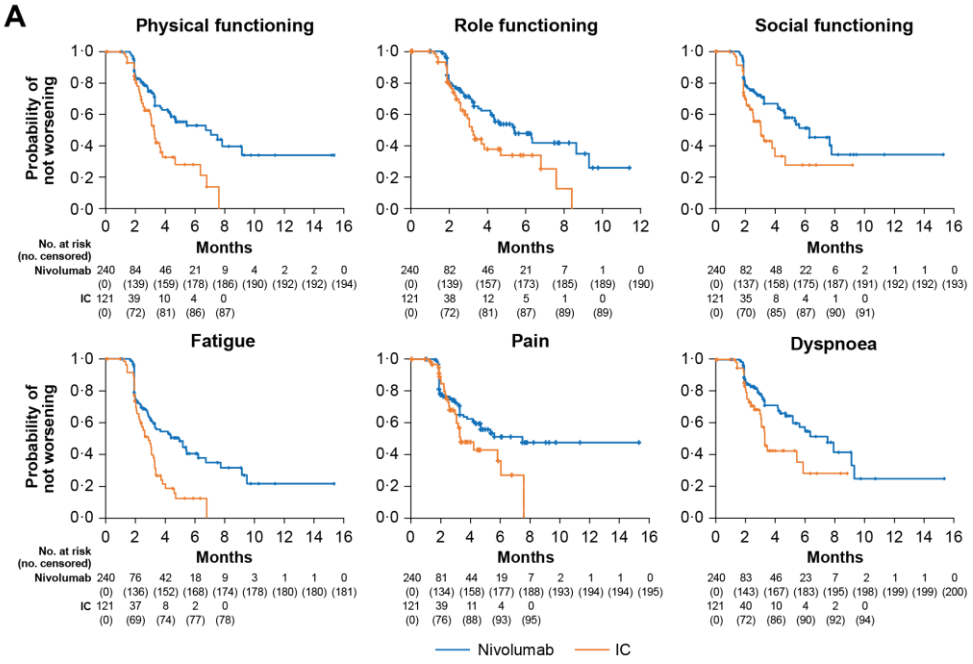


Figure 2: **Kaplan-Meier plots of time to first clinically meaningful deterioration (A) and Kaplan-Meier estimate of median time to deterioration and HR (95% CI) for the EORTC QLQ-C30 (B) among all randomised patients**

The number of evaluable patients for each timepoint, domain, and treatment group in A can be found in the appendix (p 5). EORTC QLQ-C30=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30. HR=hazard ratio. NE=not estimable. TTD=time to deterioration.



B

EORTC QLQ-C30	Nivolumab (n = 240) Events	Nivolumab (n = 240) Median (95% CI) TTD	IC (n = 121) Events	IC (n = 121) Median (95% CI) TTD	p value
Global health status	49	5·4 (4·7, 7·8)	34	3·1 (2·5, 3·7)	0·0012
Physical functioning	46	6·7 (4·3, 9·2)	34	3·3 (2·6, 3·8)	0·0014
Role functioning	50	5·4 (4·2, 9·3)	32	3·2 (2·6, 4·7)	0·018
Emotional functioning	44	5·6 (4·7, NE)	23	3·9 (3·3, 6·8)	0·15
Cognitive functioning	47	5·7 (4·2, NE)	30	3·3 (2·6, 4·7)	0·042
Social functioning	47	6·3 (4·7, NE)	30	3·1 (2·3, 4·7)	0·031
Fatigue	59	4·9 (3·2, 6·2)	43	2·8 (2·2, 3·3)	0·0014
Nausea and vomiting	30	8·3 (6·2, NE)	19	6·8 (3·5, NE)	0·16
Pain	45	7·5 (4·2, NE)	26	3·3 (3·0, 6·1)	0·23
Dyspnoea	40	7·5 (5·2, 9·3)	27	3·3 (3·0, 5·9)	0·017
Insomnia	40	7·8 (5·4, NE)	24	3·3 (3·1, NE)	0·018
Appetite loss	45	5·7 (4·4, 7·8)	25	3·3 (2·6, NE)	0·029
Constipation	33	8·3 (6·3, NE)	14	NE (3·9, NE)	0·70
Diarrhoea	30	NE (6·2, NE)	19	NE (3·3, NE)	0·090
Financial difficulties	30	NE (7·1, NE)	14	NE (3·8, NE)	0·75

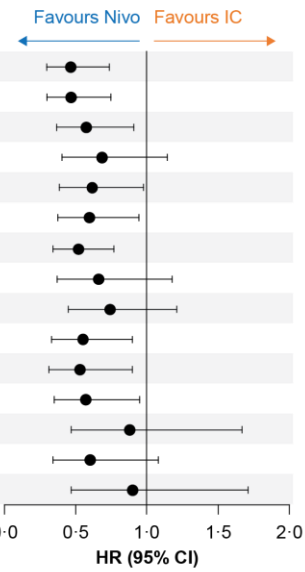


Figure 3: **EORTC QLQ-H&N35 ANCOVA**

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 groups (B). Dashed lines indicate clinically meaningful change (10 points). The number of evaluable patients for each timepoint, domain, and treatment group can be found in the appendix (p 5). EORTC QLQ-H&N35=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire head and neck cancer-specific module. *A negative value indicates an increase in weight gain.

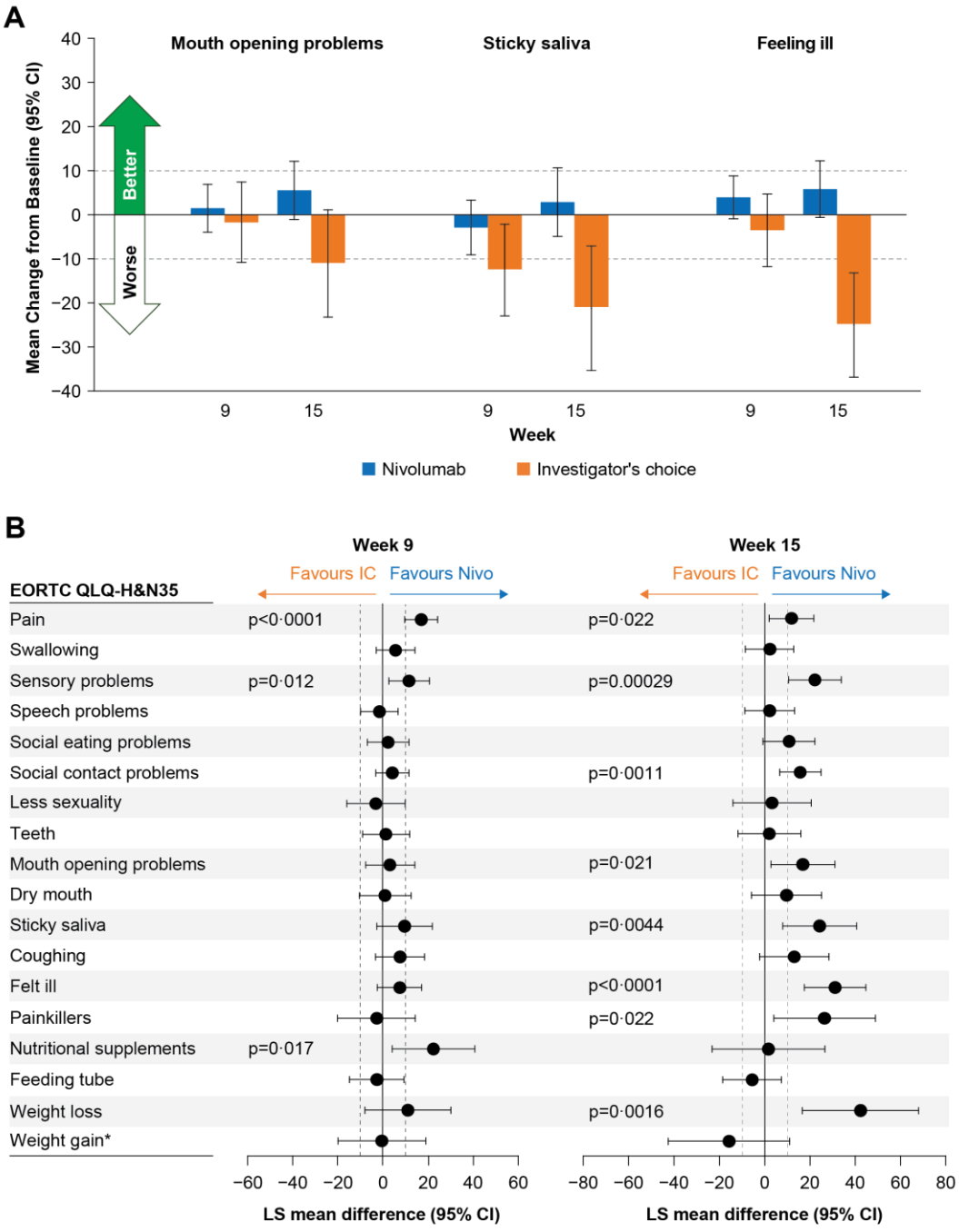
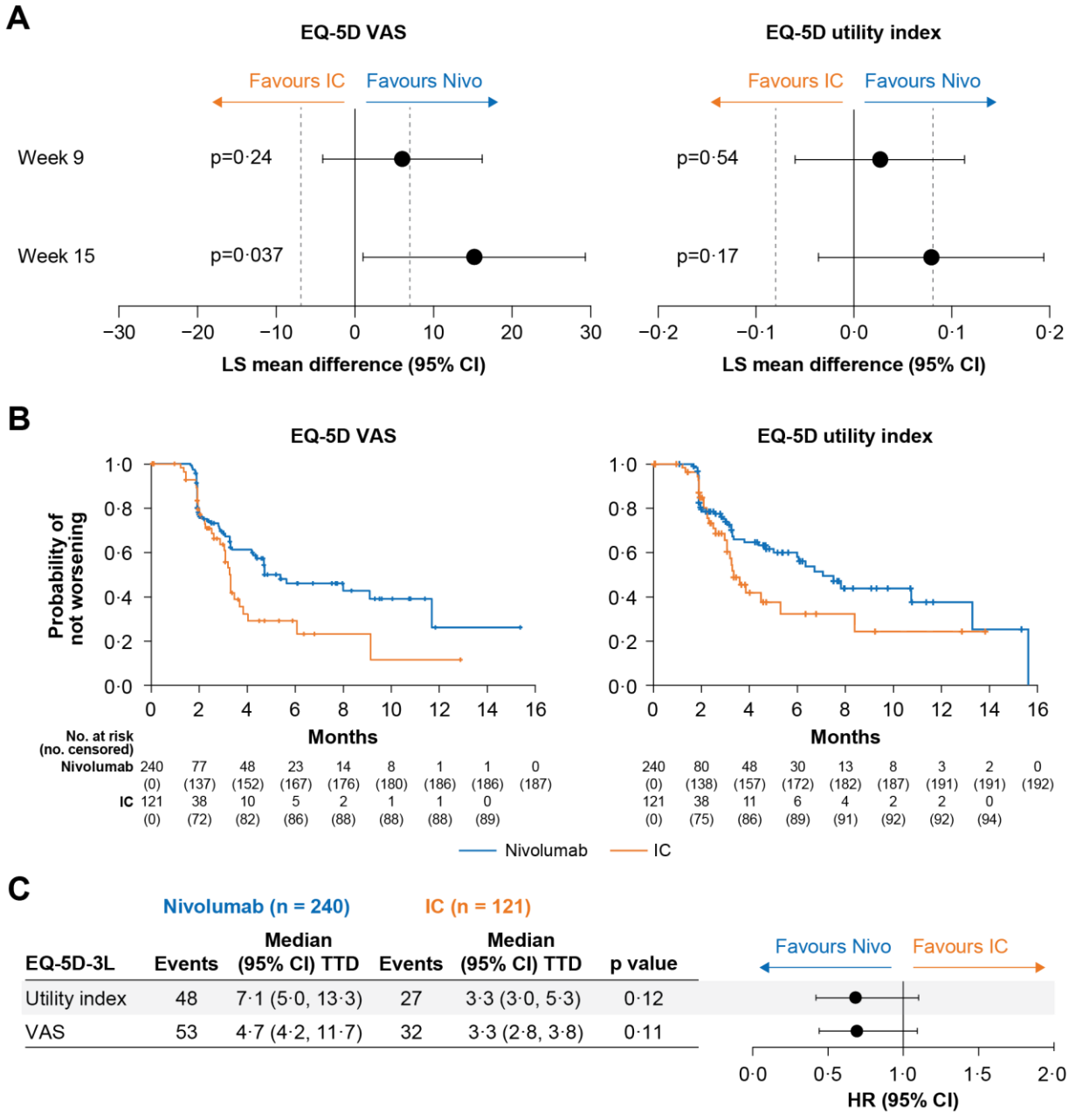


Figure 4: **EQ-5D-3L adjusted LS mean difference (95% CI) between nivolumab and investigator's choice at weeks 9 and 15 (A); and time to deterioration (Kaplan-Meier plot of time to first clinically meaningful deterioration [B]) and Kaplan-Meier estimate of median time to deterioration and HR (95% CI)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

Dashed lines in A indicate clinically meaningful change (0·08 points and 7 points for the utility index and VAS, respectively). EQ-5D-3L=three-level European Quality of Life–5 Dimensions questionnaire. HR=hazard ratio. LS=least squares. TTD=time to deterioration. VAS=visual analogue scale.



SUPPLEMENTARY APPENDIX

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

Kevin J Harrington, Robert L Ferris, George Blumenschein, Jr, A Dimitrios Colevas, Jerome Fayette, Lisa Licitra, Stefan Kasper, Caroline Even, Everett E Vokes, Francis Worden, Nabil F Saba, Naomi Kiyota, Robert Haddad, Makoto Tahara, Viktor Grünwald, James W Shaw, Manish Monga, Mark Lynch, Fiona Taylor, Michael DeRosa, Laura Morrissey, Kim Cocks, Maura L Gillison, Joel Guigay

Table S1: **Enrolment by country and site**

Country	Principal investigator	Institution	Patients Treated, n
USA	George Blumenschein, Jr	University of Texas MD Anderson	36
United Kingdom	Kevin J. Harrington	Royal Marsden NHS Foundation Trust, Royal Marsden Hospital	23
France	Jerome Fayette	Centre Leon Berard	20
France	Joel Guigay	Centre Antoine Lacassagne	19
USA	A. Dimitrios Colevas	Stanford University Medical Center	19
Italy	Lisa Licitra	IRCCS Istituto Nazionale Tumori	18
Germany	Stefan Kasper	University Hospital Essen	14
USA	Everett E. Vokes	University of Chicago	14
France	Caroline Even	Institut Gustave Roussy	13
USA	Maura L. Gillison	The Ohio State University	13
USA	Francis Worden	University of Michigan	13
USA	Nabil F. Saba	Winship Cancer Institute	10
Spain	Lara Carmen Iglesias Docampo	Hospital Universitario 12 De Octubre	8
USA	Robert Haddad	Dana-Farber Cancer Institute	8
Japan	Naomi Kiyota	Kobe University Hospital	7
Switzerland	Tamara Rordorf	Universitatsspital Zurich	7
USA	Robert L. Ferris	UPMC Cancer Center	7
United Kingdom	Shanmugasundaram Ramkumar	Southampton University Hospital NHS Trust	6
Spain	Neus Baste	Vall d'Hebron University Hospital	6
Canada	Cheryl Ho	British Columbia Cancer Agency-Vancouver Centre	6
USA	Jeffery Russell	H. Lee Moffitt Cancer Center	5
Germany	Peter Brossart	Universitaetsklinikum Bonn	5
Germany	Rainald Knecht	Uniklinikum Hamburg-Eppendorf	5
Japan	Makoto Tahara	National Cancer Center Hospital East	5
USA	Kenneth Grossmann	Huntsman Cancer Institute	5
USA	Frank Dunphy	Duke University Medical Center	5
Japan	Yasuhisa Hasegawa	Aichi Cancer Center Central Hospital	4
Japan	Shunji Takahashi	Cancer Institute Hospital	4
Spain	Juan Jose Grau	Hospital Clínic de Barcelona	4
The Netherlands	Jan Buter	Vu Medisch Centrum	4
The Netherlands	S. J. Oosting	Universitair Medisch Centrum Groningen	3
United Kingdom	Andrew Sykes	Christie Hospital	3
Argentina	Mirta Susana Varela	Centro de Oncología e Investigación de Buenos Aires	3
Taiwan	Chia-Jui Yen	National Cheng Kung University Hospital	3
Italy	Mario Airoldi	Azienda Ospedaliera Citta della Salute e della Scienza	2
USA	Thomas Cosgriff	Crescent City Research Consortium, LLC	2
Germany	Viktor Gruenwald	Med Hochschule Hannover	2
Taiwan	Ruey-Long Hong	National Taiwan University Hospital	2
United Kingdom	David Husband	Clatterbridge Hospital	2
Italy	Franco Ionna	Istituto Nazionale Tumori Fondazione Pascale	2
Japan	Shigemichi Iwae	Hyogo Cancer Center	2
Japan	Yasushi Shimizu	Hokkaido University Hospital	2
Japan	Tomoya Yokota	Shizuoka Cancer Center	2
Italy	Haralabos Koussis	Istituto Oncologico Veneto IOV - IRCCS	2
Brazil	Carlos Henrique Barrios	Hospital São Lucas da PUCRS	2
Italy	Daris Ferrari	Azienda Ospedaliera San Paolo	1
USA	Jill Gilbert	Vanderbilt Cancer Clinic	1
Japan	Masahiro Goto	Osaka Medical College Hospital	1
Republic of Korea	Jin-Hyoung Kang	The Catholic University of Korea, Seoul St. Mary's Hospital	1
Germany	Ulrich Keilholz	Charité Universitätsmedizin Berlin	1
Hong Kong	Wing Sum Kenneth Li	Queen Elizabeth Hospital	1
Argentina	Martin Eduardo Richardet	Instituto Oncologico De Cordoba	1
Germany	Urs Mueller-Richter	Klinikum der Universitaet Würzburg	1

Table S2: **Completion rates for patient-reported outcome measures**

Pro measure/ Week	NIVOLUMAB			INVESTIGATOR'S CHOICE		
	Forms received	Patients on study	Completed (%)	Forms received	Patients on study	Completed (%)
EORTC QLQ-C30						
0	191	240	79·6	91	121	75·2
9	105	131	80·2	34	57	59·7
15	58	85	68·2	16	30	53·3
21	48	58	82·8	7	14	50·0
27	31	44	70·5	2	5	40·0
33	21	30	70·0	3	3	100·0
39	10	19	52·6	1	1	100·0
45	11	15	73·3	0	0	NA
51	6	9	66·7	0	0	NA
57	3	5	60·0	0	0	NA
69	2	2	100·0	0	0	NA
EORTC QLQ-H&N35						
0	193	240	80·4	91	121	75·2
9	104	131	79·4	36	56*	64·3
15	58	85	68·2	15	30	50·0
21	47	58	81·0	7	14	50·0
27	31	44	70·5	2	5	40·0
33	21	30	70·0	3	3	100·0
39	9	19	47·4	1	1	100·0
45	11	15	73·3	0	0	NA
51	6	9	66·7	0	0	NA
57	3	5	60·0	0	0	NA
69	1	1	100·0	0	0	NA
EQ-5D-3L						
0	191	240	79·6	90	121	74·4
9	103	131	78·6	35	57	61·4
15	58	85	68·2	16	30	53·3
21	48	58	82·8	7	14	50·0
27	31	44	70·5	2	5	40·0
33	21	30	70·0	2	3	66·7
39	9	19	47·4	1	1	100·0
45	11	15	73·3	0	0	NA
51	6	9	66·7	0	0	NA
57	3	5	60·0	0	0	NA
69	2	2	100·0	0	0	NA

*One patient in the investigator's choice arm met eligibility criteria for completing the EORTC QLQ-C30 but not the QLQ-H&N35 at week 9. Accordingly, the number of on-study patients in the investigator's choice arm is listed as being different for the 2 measures. EORTC QLQ-C30=European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire–Core 30. EORTC QLQ-H&N35=European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire head and neck cancer–specific module. EQ-5D-3L=three-level European Quality of Life–5 Dimensions questionnaire; NA=not applicable; PRO=patient-reported outcome.

Table S3: **Baseline characteristics among patients included in ANCOVA analyses**

Characteristic	Nivolumab (n=93)	Investigator's choice (n=36)
Age, median (range), years	61·0 (29·0–78·0)*	58·0 (39·0–74·0)
<65 years, n (%)	62 (66·7)	23 (63·9)
Race, n (%)		
White	73 (78·5)	33 (91·7)
Asian	16 (17·2)	3 (8·3)
Other	4 (4·3)	0
ECOG performance status, n (%)		
0	24 (25·8)	11 (30·6)
1	69 (74·2)	25 (69·4)
Number of lines of prior chemotherapy in the metastatic setting, n (%)		
0	44 (47·3)	15 (41·7)
1	35 (37·6)	10 (27·8)
2	11 (11·8)	8 (22·2)
≥3	3 (3·2)	3 (8·3)
PD-L1 expression		
≥1%	35 (37·6)	18 (50·0)
<1%	29 (31·2)	13 (36·1)
Not determined	29 (31·2)	5 (13·9)
Smoking or tobacco use, n (%)		
Current or former	72 (77·4)	27 (75·0)
Never	19 (20·4)	8 (22·2)
Not reported	2 (2·2)	1 (2·8)
Prior cetuximab treatment, n (%)	52 (55·9)	20 (55·6)

* Based on available data (n=89). ANCOVA=analysis of covariance. ECOG=Eastern Cooperative Oncology Group. PD-L1=programmed death ligand 1.

Table S4: **Baseline mean (SD) and LS mean (95% CI) change from baseline at weeks 9 and 15 among patients with baseline and ≥1 post-baseline assessment**

Questionnaire	**Baseline***				**Week 9**				**Week 15**			
Item	**Nivolumab**		**Investigator's choice**		**Nivolumab**		**Investigator's choice**		**Nivolumab**		**Investigator's choice**	
EORTC QLQ-C30[†] **(n = 127)**	**n**	**Mean (SD)**	**n**	**Mean (SD)**	**n**	**LS mean (95% CI) change**	**n**	**LS mean (95% CI) change**	**n**	**LS mean (95% CI) change**	**n**	**LS mean (95% CI) change**
Global health status	89	60·3 (21·4)	36	61·8 (18·7)	83	2·4 (4·1)	30	−5·8 (6·7)[‡]	44	2·7 (5·3)	13	−7·3 (10·0)[‡]
Physical functioning	89	81·0 (18·5)	36	76·7 (24·5)	84	1·3 (2·9)	30	−6·0 (4·9)[‡]	43	−1·9 (3·9)	14	**−19·9 (6·9)**[§]
Role functioning	88	76·1 (27·2)	36	69·0 (33·4)	83	4·9 (4·9)	29	−9·7 (8·2)[‡]	42	−0·3 (5·9)	14	**−23·8 (10·4)**[§]
Emotional functioning	90	80·2 (18·7)	36	81·3 (18·6)	84	1·0 (3·5)	30	−7·2 (5·7)[‡]	44	−1·9 (4·3)	13	−9·9 (8·0)[‡]
Cognitive functioning	90	87·0 (18·8)	36	90·3 (14·0)	84	1·8 (3·5)	30	−4·9 (5·7)[‡]	44	−1·3 (4·5)[‡]	13	**−16·0 (8·2)**[‖]
Social functioning	89	73·6 (28·8)	36	76·9 (29·9)	83	5·3 (4·5)[¶]	30	−8·5 (7·2)[‡]	44	5·4 (5·5)[¶]	13	**−15·8 (10·2)**[‖]
Fatigue	89	32·4 (23·7)	36	34·9 (21·6)	84	4·1 (4·1)	30	−6·6 (6·7)[‡]	43	1·1 (4·9)	14	**−21·8 (8·6)**[§]
Nausea and vomiting	89	6·0 (11·0)	36	7·4 (13·5)	84	0·2 (3·3)	30	−3·9 (5·5)	43	−2·1 (4·5)	14	−9·9 (8·0)[‡]
Pain	91	31·3 (27·3)	36	29·2 (29·1)	86	4·0 (4·9)	30	2·2 (8·0)	44	2·6 (6·3)	14	−9·8 (11·4)[‡]
Dyspnoea	89	17·2 (24·2)	36	18·5 (25·8)	83	3·0 (4·3)[¶]	30	−7·5 (7·2)[‡]	43	1·5 (5·9)	14	**−23·7 (10·4)**[‖]
Insomnia	89	22·5 (27·4)	36	24·1 (28·3)	83	2·2 (5·1)	30	−4·1 (8·4)[‡]	43	4·4 (6·5)	14	**−24·5 (11·6)**[§]
Appetite loss	89	22·8 (29·6)	36	31·5 (36·5)	84	2·1 (5·9)	30	**−10·1 (9·8)**[‡]	43	2·2 (7·6)	14	**−20·9 (13·5)**[‖]
Constipation	90	18·1 (26·5)	36	25·9 (33·0)	84	5·3 (4·9)[¶]	30	−2·9 (8·0)	44	3·4 (5·9)	13	2·4 (10·6)
Diarrhoea	90	7·4 (19·8)	36	4·6 (11·7)	84	1·6 (3·3)	30	−9·3 (5·3)[‡]	44	1·2 (4·1)	13	−5·9 (7·8)[‡]
Financial difficulties	90	*18·9 (24·5)*	36	*31·5 (36·5)*	84	1·1 (4·7)	29	1·2 (8·0)	44	0 (5·7)	13	−3·7 (10·6)[‡]
EORTC QLQ-H&N35[†] **(n = 128)**	**n**	**Mean (SD)**	**n**	**Mean (SD)**	**n**	**LS mean (95% CI) change**	**n**	**LS mean (95% CI) change**	**n**	**LS mean (95% CI) change**	**n**	**LS mean (95% CI) change**
Pain	92	23·4 (23·9)	36	24·8 (28·6)	85	4·4 (3·7)	30	**−12·6 (6·3)**	46	5·0 (4·7)	14	−6·7 (8·6)
Swallowing problems	92	26·1 (27·5)	35	24·5 (21·9)	83	0·1 (4·3)	29	−5·5 (7·2)	46	−3·2 (5·1)	13	−5·1 (9·2)
Sensory problems	91	25·1 (27·9)	36	23·1 (26·8)	84	4·4 (4·5)	29	−7·3 (7·6)	45	3·7 (5·5)	14	**−18·2 (10·0)**
Speech problems	88	30·3 (26·4)	35	27·9 (30·7)	80	0·8 (4·3)	28	2·4 (7·0)	44	2·1 (5·3)	14	0 (9·4)
Social eating problems	89	*26·4 (29·2)*	35	*38·8 (27·6)*	79	0·6 (4·7)	28	−1·6 (7·8)	45	−1·0 (5·5)	14	**−11·5 (9·8)**
Social contact problems	89	16·1 (22·7)	36	15·9 (19·8)	81	1·2 (3·7)	29	−3·0 (6·1)	45	1·8 (4·5)	14	**−13·7 (7·8)**
Less sexuality	87	44·3 (38·3)	35	42·4 (40·3)	80	−0·1 (6·7)	29	3·0 (11·0)	42	4·5 (8·2)	13	1·4 (14·9)
Teeth problems	89	*16·9 (28·9)*	36	*26·9 (37·2)*	82	0·8 (5·3)	29	−0·6 (8·8)	45	1·9 (5·9)	13	0 (12·2)
Mouth opening problems	92	34·4 (38·1)	36	38·9 (36·9)	83	1·5 (5·5)	30	−1·7 (9·2)	46	5·6 (6·7)	14	**−11·0 (12·2)**
Dry mouth	92	*38·4 (36·0)*	36	*54·6 (35·8)*	85	−0·8 (5·7)	30	−1·8 (9·6)	46	9·3 (7·2)	14	−0·2 (13·3)
Sticky saliva	91	35·5 (34·7)	36	38·0 (34·9)	84	−2·9 (6·3)	29	**−12·5 (10·4)**	45	2·9 (7·8)	14	**−21·1 (14·1)**
Coughing	92	29·7 (29·4)	36	32·4 (30·3)	85	0·8 (5·5)	30	−6·8 (9·2)	46	4·6 (7·2)	14	−8·3 (13·1)
Feeling ill	92	21·0 (26·9)	36	18·5 (29·2)	85	4·0 (4·9)	30	−3·5 (8·2)	46	5·9 (6·5)	14	**−25·0 (11·8)**
Painkiller use	90	*72·2 (45·0)*	36	*61·1 (49·4)*	83	**10·6 (8·8)**	29	**13·4 (14·5)**	45	**13·8 (10·8)**	14	**−12·5 (19·4)**
Nutritional supplement use	89	43·8 (49·9)	36	47·2 (50·6)	82	0·8 (9·2)	29	**−21·6 (15·5)**	44	−4·1 (12·0)	14	−5·6 (21·4)
Feeding tube	90	27·8 (45·0)	36	22·2 (42·2)	83	0·2 (6·3)	29	3·0 (10·2)	45	−1·9 (6·5)	14	3·9 (11·0)
Weight loss	89	36·0 (48·3)	36	33·3 (47·8)	82	5·0 (9·6)	29	−6·1 (16·1)	44	**15·3 (12·3)**	14	**−26·8 (22·1)**
Weight gain[#]	89	21·3 (41·2)	36	25·0 (43·9)	81	**−13·2 (9·8)**	29	**−12·8 (16·5)**	41	**−15·2 (12·7)**	13	0·8 (22·9)
EQ-5D-3L (n = 124)	**n**	**Mean (SD)**	**n**	**Mean (SD)**	**n**	**LS mean (95% CI) change**	**n**	**LS mean (95% CI) change**	**n**	**LS mean (95% CI) change**	**n**	**LS mean (95% CI) change**
Utility index	87	0·69 (0·28)	33	0·65 (0·27)	81	0·06 (0·04)	27	0·03 (0·07)	42	0·05 (0·06)	14	−0·03 (0·10)
VAS	89	55·8 (28·0)	33	62·6 (28·2)	83	3·6 (4·9)	27	−2·4 (8·6)	44	**7·3 (6·7)**	13	**−7·8 (12·3)**

Italic typeface indicates clinically meaningful difference between arms in baseline score and bold typeface indicates clinically meaningful change from baseline (≥10 points for the EORTC domains, ≥0·08 points for the EQ-5D utility index, and ≥7 points for the EQ-5D VAS). CI=confidence interval. EORTC QLQ-

C30=European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire–Core 30. EORTC QLQ-H&N35=European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire head and neck cancer–specific module. EQ-5D-3L=three-level European Quality of Life–5 Dimensions questionnaire. LS=least squares. QoL=quality of life. SD=standard deviation. VAS=visual analogue scale. *For the EQ-5D-3L VAS and EORTC QLQ-C30 functional and global health/QoL scales, higher baseline values are better. For all other scales, higher baseline values indicate a higher level of symptomatology or problems. †For simplification of presentation, all changes from baseline have been ordered such that a positive value indicates improvement and a negative value indicates deterioration. ‡Indicates small clinically meaningful deterioration based on thresholds from Cocks et al.[32] §Indicates large clinically meaningful deterioration based on thresholds from Cocks et al.[32] ǁIndicates medium clinically meaningful deterioration based on thresholds from Cocks et al.[32] ¶Indicates small clinically meaningful improvement based on thresholds from Cocks et al.[32] #A negative value indicates an increase in weight gain.

Figure S1: **Adjusted mean change from baseline at weeks 9 and 15 in EORTC QLQ-C30 domains overall and by baseline PD-L1 expression**

Dashed lines indicate clinically meaningful difference (10 points). 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. PD-L1=programmed death ligand 1.

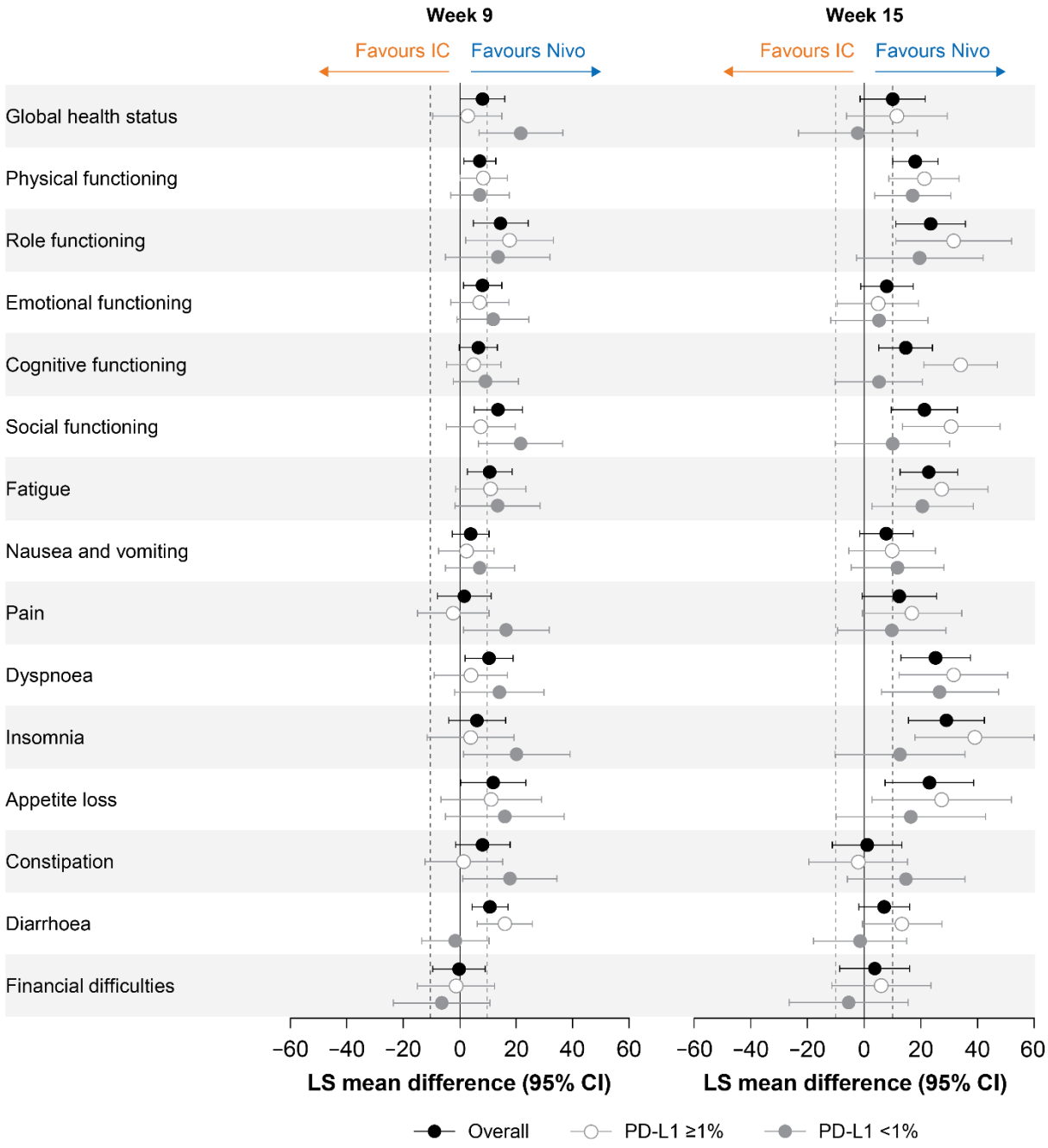


Figure S2: **Adjusted least squares mean change from baseline at weeks 9 and 15 in EORTC QLQ-C30 domains overall and by baseline p16 status**

Dashed lines indicate clinically meaningful difference (10 points). 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.

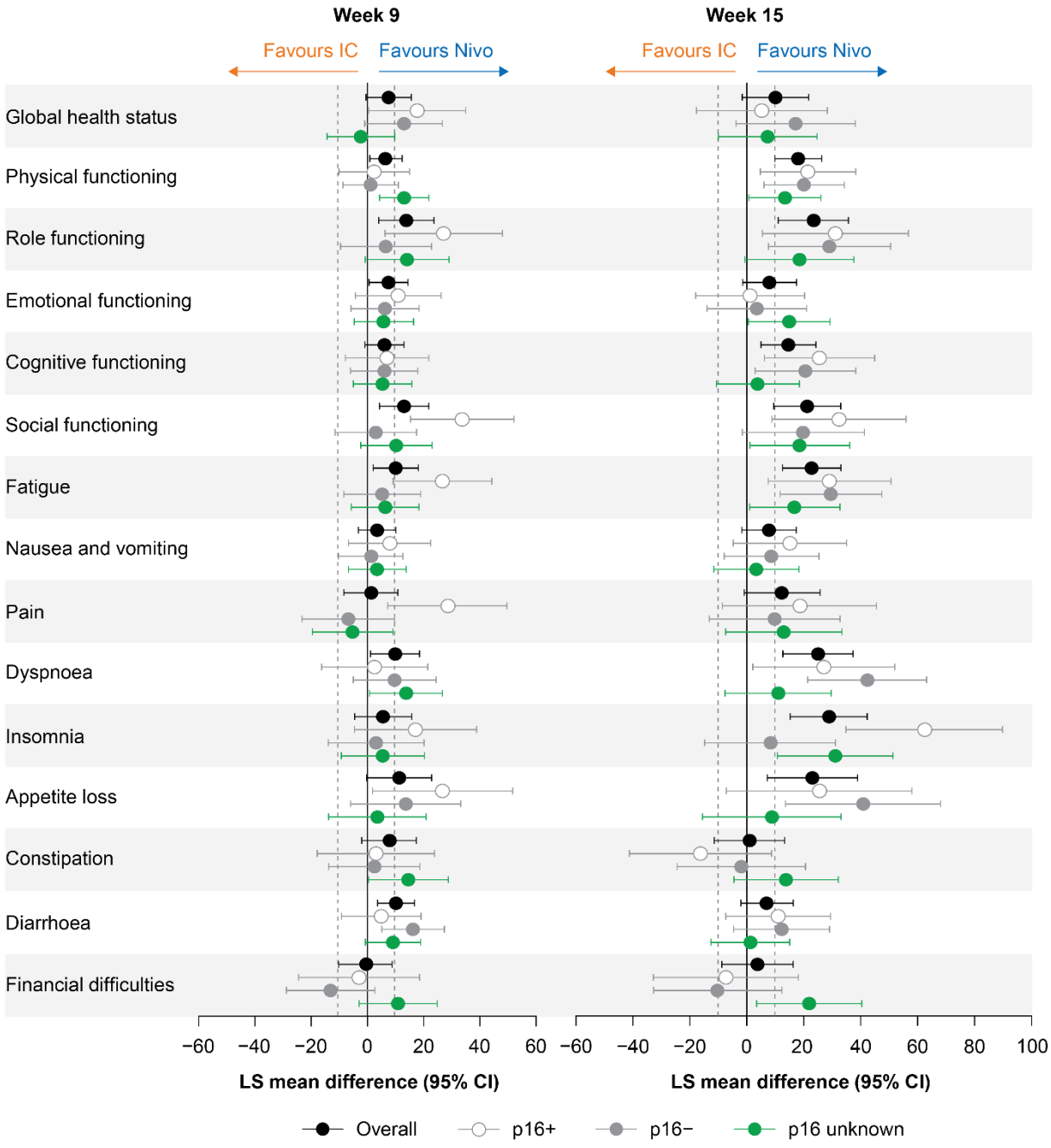


Figure S3: **Kaplan-Meier plots of time to first clinically meaningful deterioration for additional domains of the EORTC QLQ-C30 among all randomised patients**

EORTC QLQ-C30=European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire–Core 30. IC=investigator's choice.

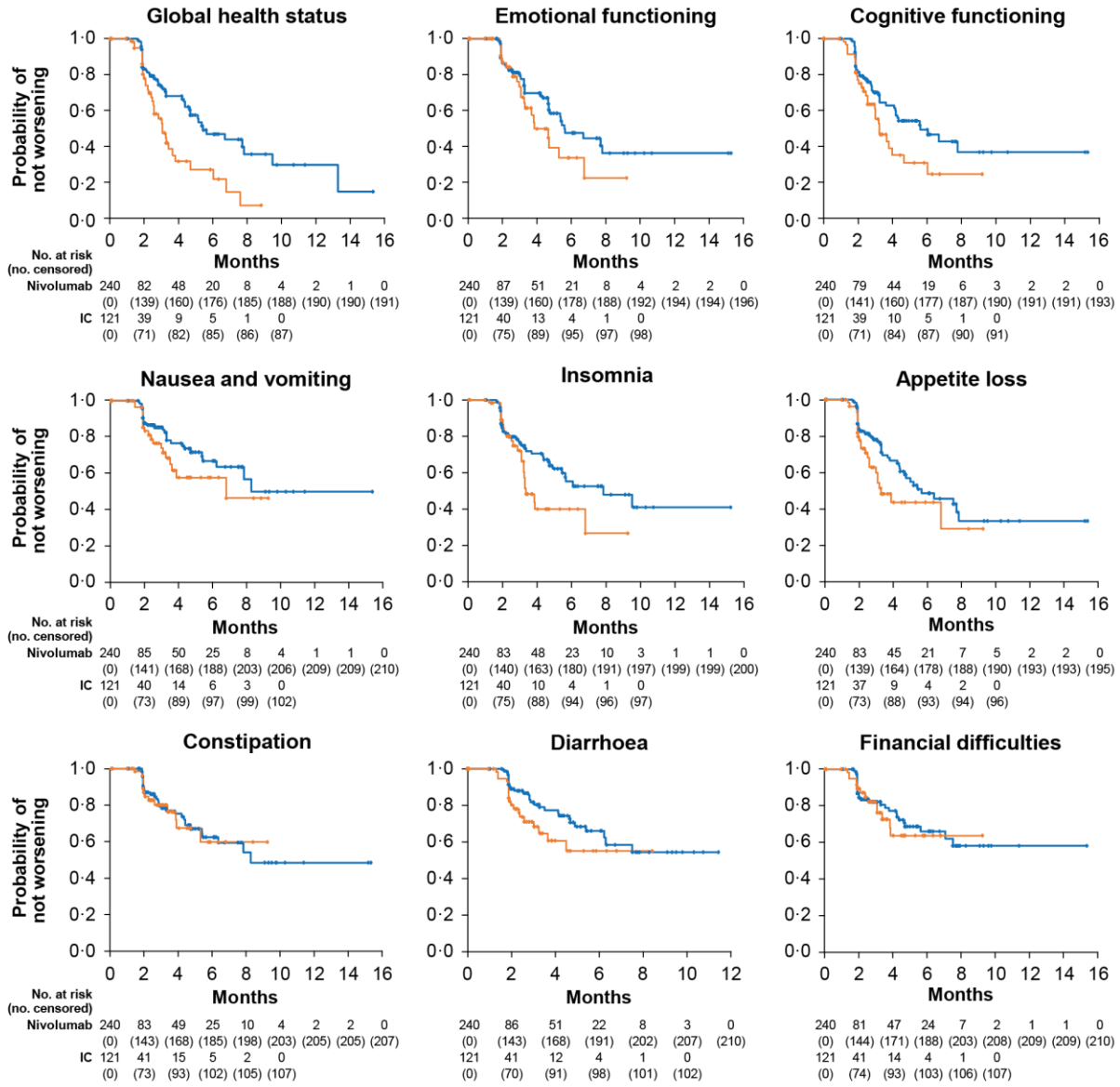


Figure S4: **Adjusted mean change from baseline at weeks 9 and 15 in EORTC QLQ-H&N35 domains overall and by PD-L1 expression**

Dashed lines indicate clinically meaningful difference (10 points). CI=confidence interval. EORTC QLQ-C30=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. PD-L1=programmed death ligand 1. *A

negative value indicates an increase in weight gain.

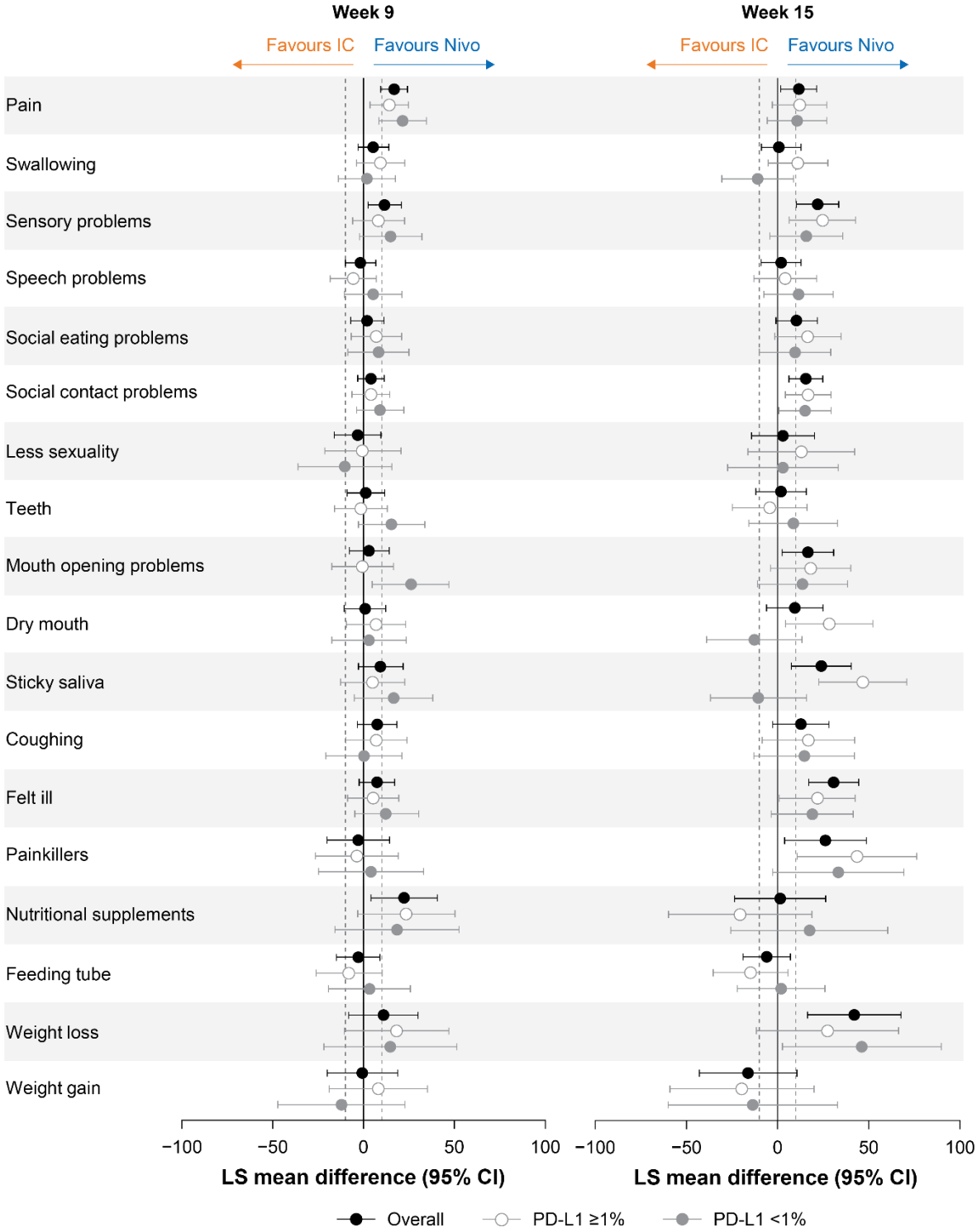


Figure S5: **Adjusted mean change from baseline at weeks 9 and 15 in EORTC QLQ-H&N35 domains overall and by p16 status**

Dashed lines indicate clinically meaningful difference (10 points). 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. LS=least squares. Nivo= nivolumab. *A negative value indicates an increase in weight gain.

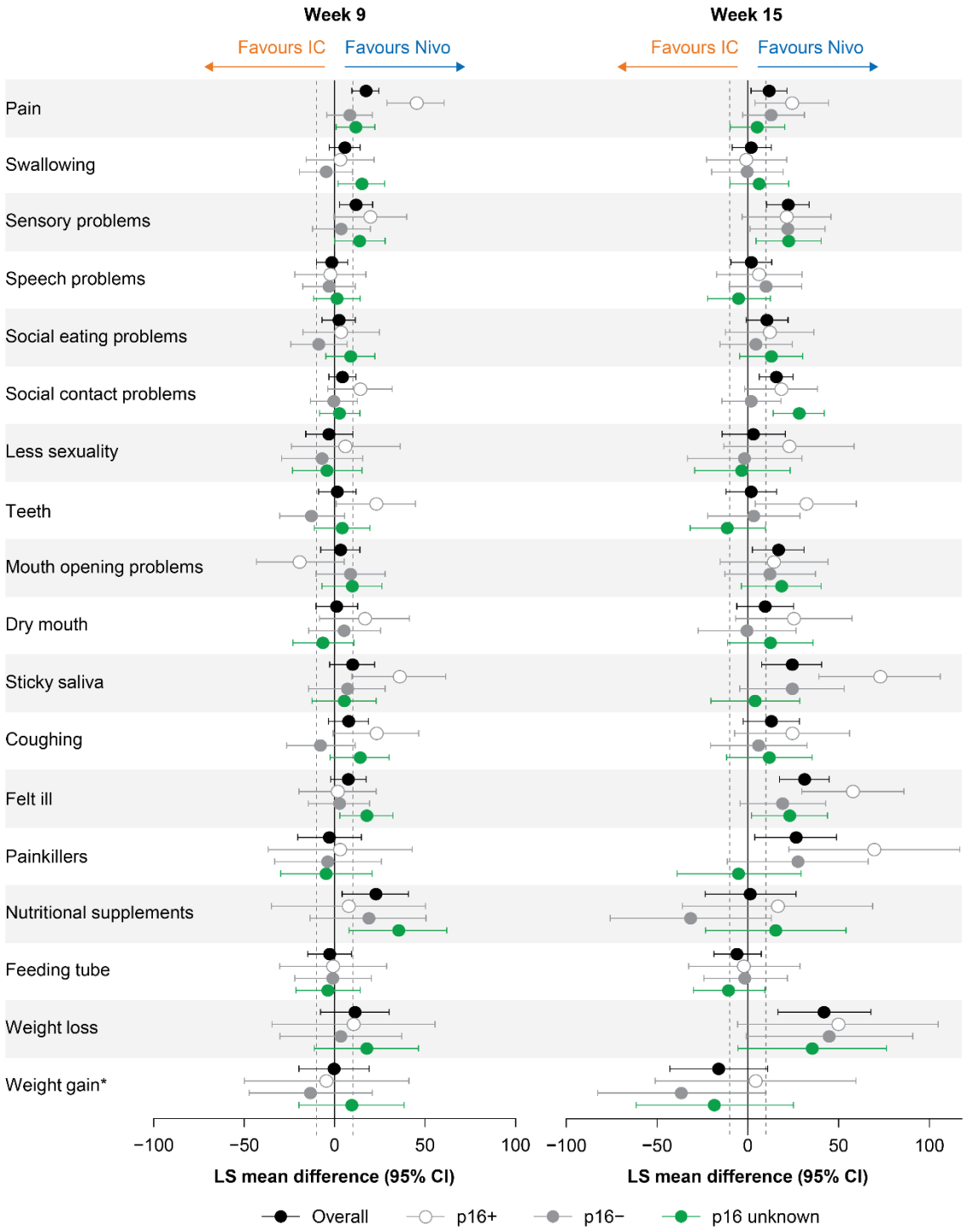
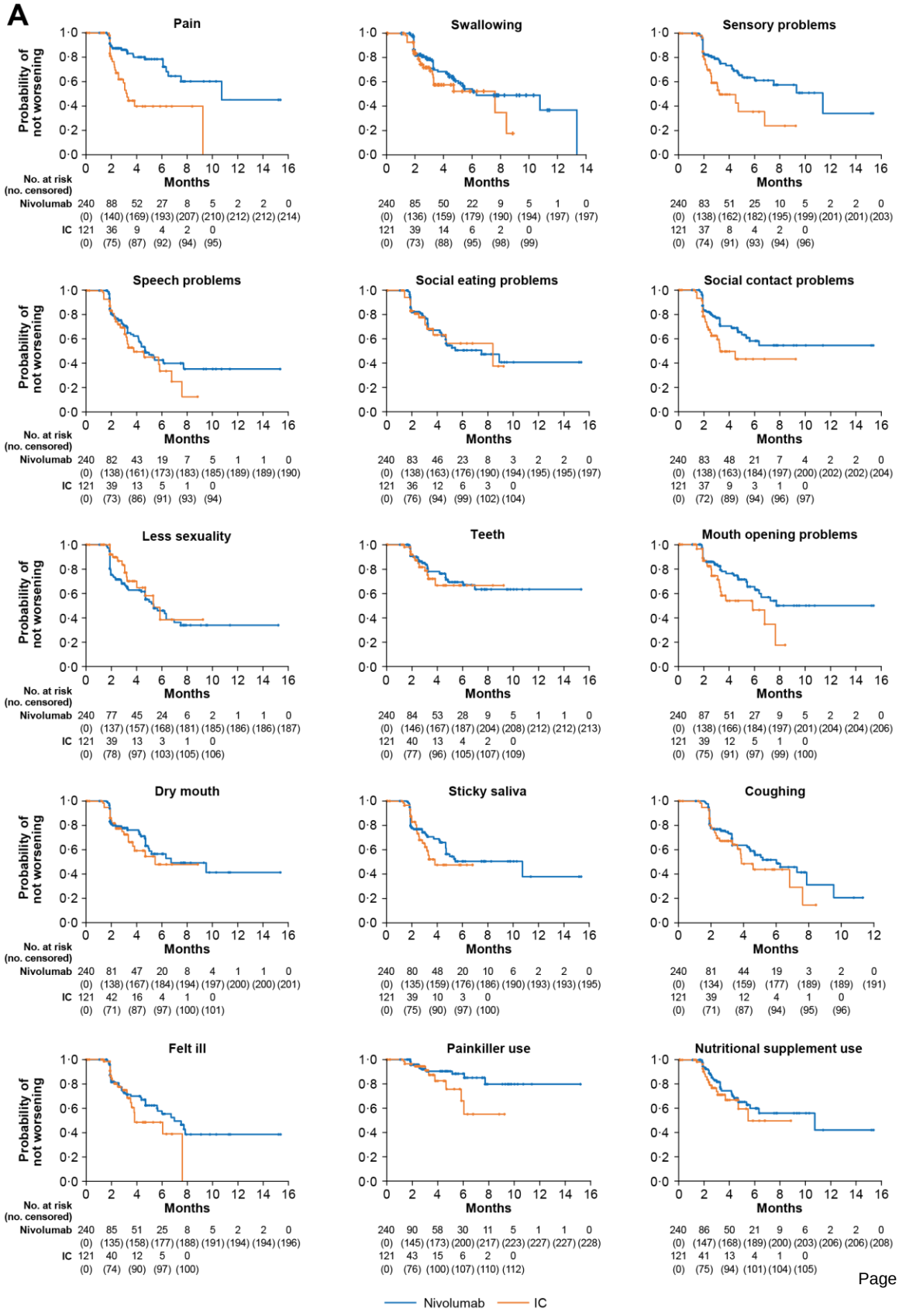
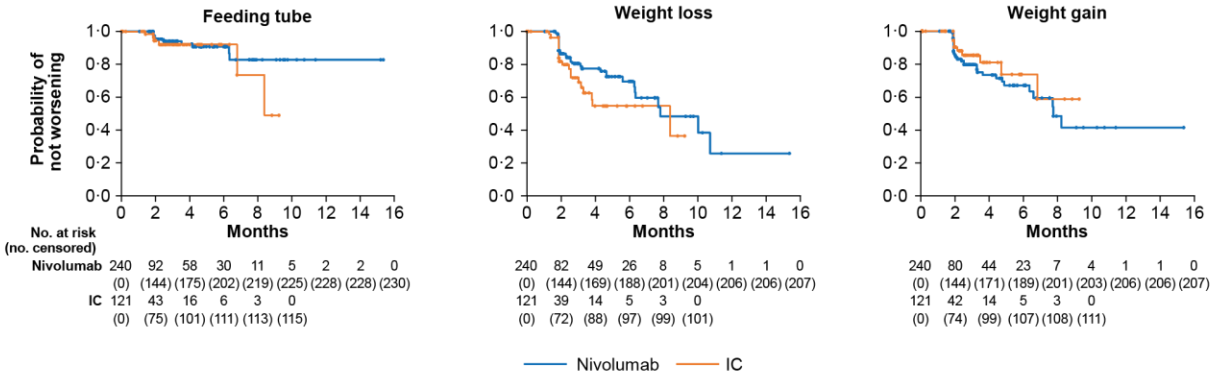


Figure S6: **Time to deterioration (Kaplan-Meier plots of time to first clinically meaningful deterioration, A) and Kaplan-Meier estimate of median time to deterioration and HR (95% CI) for the EORTC QLQ-H&N35 (B) among all randomised patients**

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. HR=hazard ratio. IC=investigator's choice. NE=not estimable. Nivo=nivolumab. TTD=time to deterioration.


A
Pain
Swallowing
Sensory problems
Speech problems
Social eating problems
Social contact problems
Less sexuality
Teeth
Mouth opening problems
Dry mouth
Sticky saliva
Coughing
Felt ill
Painkiller use
Nutritional supplement use
Probability of not worsening
Months
No. at risk (no. censored)
Nivolumab
IC
Nivolumab
IC



B

EORTC QLQ-H&N35	Nivolumab (n = 240) Events	Median (95% CI) TTD	IC (n = 121) Events	Median (95% CI) TTD	p value
Pain	26	10·7 (6·5, NE)	26	3·3 (2·6, 9·2)	<0·0001
Swallowing	43	6·3 (4·7, 13·3)	22	7·6 (3·3, NE)	0·27
Sensory problems	37	11·4 (6·0, NE)	25	3·2 (2·6, 6·8)	0·0060
Speech problems	50	4·7 (4·1, 7·7)	27	3·8 (3·1, 6·8)	0·34
Social eating problems	43	7·5 (4·7, NE)	17	8·4 (3·7, NE)	0·41
Social contact problems	36	NE (5·3, NE)	24	3·3 (2·6, NE)	0·041
Less sexuality	53	5·3 (4·7, 7·0)	15	5·3 (4·0, NE)	0·18
Teeth	27	NE (7·0, NE)	12	NE (3·9, NE)	0·43
Mouth opening problems	34	7·7 (6·0, NE)	21	5·8 (3·2, 7·6)	0·023
Dry mouth	39	6·7 (4·9, NE)	20	5·5 (3·7, NE)	0·15
Sticky saliva	45	10·7 (4·7, NE)	21	3·8 (2·8, NE)	0·19
Coughing	49	6·0 (4·3, 9·5)	25	3·9 (3·3, 7·6)	0·23
Felt ill	44	7·0 (5·6, NE)	21	3·9 (3·5, 7·6)	0·31
Painkillers	12	NE (NE, NE)	9	NE (5·8, NE)	0·36
Nutritional supplements	32	10·7 (5·6, NE)	16	5·5 (3·7, NE)	0·080
Feeding tube	10	NE (NE, NE)	6	8·4 (6·8, NE)	0·44
Weight loss	33	7·8 (6·3, NE)	20	8·4 (3·2, NE)	0·070
Weight gain	33	7·7 (6·3, NE)	10	NE (6·8, NE)	0·24