

Nivolumab Improved Survival For Patients With Head and Neck Squamous Cell Carcinoma

NEW ORLEANS — Treatment with the immunotherapeutic nivolumab (Opdivo) improved survival for patients with recurrent or metastatic head and neck squamous cell carcinoma that progressed after platinum-based chemotherapy compared with single-agent chemotherapy of the investigator's choice, according to results from the CheckMate-141 phase III clinical trial presented here at the AACR Annual Meeting 2016, April 16-20.

“Recurrent or metastatic head and neck squamous cell carcinoma that is not responsive to platinum-based chemotherapy progresses very rapidly, and patients have a very poor prognosis,” said Maura L. Gillison, MD, PhD, a professor in the Department of Internal Medicine at The Ohio State University Comprehensive Cancer Center – Arthur G. James Cancer Hospital and Richard J. Solove Research Institute. “Treatment usually involves single-agent chemotherapy. However, no therapy has been shown to improve survival for this patient population. New treatment options are desperately needed.

“This study is the first randomized clinical trial to clearly demonstrate improved overall survival for patients with platinum-refractory recurrent or metastatic head and neck squamous cell carcinoma,” continued Gillison. “We hope that the results will establish nivolumab as a new standard of care option for this patient population and thereby fulfill a huge unmet need.”



CheckMate-141 was a randomized, phase III clinical trial designed to determine whether the PD-1 inhibitor nivolumab could extend overall survival for patients with platinum-refractory recurrent or metastatic head and neck squamous cell carcinoma compared with treatment of the investigator's choice, which was any of the commonly used therapeutics docetaxel, methotrexate, or cetuximab.

Of the 361 patients enrolled in the clinical trial, 240 were randomly assigned to nivolumab and 121 to single-agent chemotherapy of investigator's choice.

At the interim analysis, which was conducted after 218 events, patients assigned to nivolumab were found to have a 30 percent reduction in risk of death compared with those assigned therapy of investigator's choice. Median overall survival was 7.5 months for those assigned nivolumab versus 5.1 months for those assigned therapy of investigator's choice. At 12 months, 36 percent of the patients treated with nivolumab were alive compared with 17 percent of those assigned therapy of investigator's choice.

Because certain types of head and neck squamous cell carcinoma, particularly those arising in the oropharynx (back of the throat, including the base of the tongue and tonsils), have been linked with human papillomavirus (HPV) infection, the investigators also evaluated the data based on the HPV status of the patients' tumors.

The effect of nivolumab on overall survival was seen for both patients with HPV-positive disease and those with HPV-negative disease. Among patients with HPV-positive disease, median overall survival was 9.1 months for those assigned nivolumab versus 4.4 months for those assigned therapy of investigator's choice, and among patients with HPV-negative disease, median overall survival was 7.5 months for those assigned nivolumab versus 5.8 months for those assigned therapy of investigator's choice.

A survival benefit in patients treated with nivolumab was observed for the overall study population. Exploratory analysis suggested that the benefit was greater for patients treated with nivolumab whose tumors had PD-L1 expression (of 1 percent or greater) or were HPV-positive.

“Overall, our data are extremely exciting. This clinical trial has established head and neck squamous cell carcinoma as responsive to immunotherapy. We are hopeful that this represents the tip of the iceberg with regard to future benefit of immunotherapy for patients with head and neck squamous cell carcinoma,” added Gillison.

This study was funded by Bristol-Myers Squibb. Gillison's role in the study was funded in part by the Oral Cancer Foundation. Gillison has consulted for Bristol-Myers Squibb, Eli Lilly and Company, and Merck in the past year.

ORIGINAL ARTICLE

Nivolumab for Recurrent Squamous-Cell Carcinoma of the Head and Neck

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ABSTRACT

BACKGROUND

Patients with recurrent or metastatic squamous-cell carcinoma of the head and neck after platinum chemotherapy have a very poor prognosis and limited therapeutic options. Nivolumab, an anti-programmed death 1 (PD-1) monoclonal antibody, was assessed as treatment for this condition.

METHODS

In this randomized, open-label, phase 3 trial, we assigned, in a 2:1 ratio, 361 patients with recurrent squamous-cell carcinoma of the head and neck whose disease had progressed within 6 months after platinum-based chemotherapy to receive nivolumab (at a dose of 3 mg per kilogram of body weight) every 2 weeks or standard, single-agent systemic therapy (methotrexate, docetaxel, or cetuximab). The primary end point was overall survival. Additional end points included progression-free survival, rate of objective response, safety, and patient-reported quality of life.

RESULTS

The median overall survival was 7.5 months (95% confidence interval [CI], 5.5 to 9.1) in the nivolumab group versus 5.1 months (95% CI, 4.0 to 6.0) in the group that received standard therapy. Overall survival was significantly longer with nivolumab than with standard therapy (hazard ratio for death, 0.70; 97.73% CI, 0.51 to 0.96; $P=0.01$), and the estimates of the 1-year survival rate were approximately 19 percentage points higher with nivolumab than with standard therapy (36.0% vs. 16.6%). The median progression-free survival was 2.0 months (95% CI, 1.9 to 2.1) with nivolumab versus 2.3 months (95% CI, 1.9 to 3.1) with standard therapy (hazard ratio for disease progression or death, 0.89; 95% CI, 0.70 to 1.13; $P=0.32$). The rate of progression-free survival at 6 months was 19.7% with nivolumab versus 9.9% with standard therapy. The response rate was 13.3% in the nivolumab group versus 5.8% in the standard-therapy group. Treatment-related adverse events of grade 3 or 4 occurred in 13.1% of the patients in the nivolumab group versus 35.1% of those in the standard-therapy group. Physical, role, and social functioning was stable in the nivolumab group, whereas it was meaningfully worse in the standard-therapy group.

CONCLUSIONS

Among patients with platinum-refractory, recurrent squamous-cell carcinoma of the head and neck, treatment with nivolumab resulted in longer overall survival than treatment with standard, single-agent therapy. (Funded by Bristol-Myers Squibb; CheckMate 141 ClinicalTrials.gov number, NCT02105636.)

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SQUAMOUS-CELL CARCINOMA OF THE HEAD and neck is a major cause of cancer-associated illness and death, with more than 600,000 cases diagnosed annually worldwide.¹ Most patients present with locoregionally advanced disease, and more than 50% have recurrence within 3 years.²⁻⁴ Patients with squamous-cell carcinoma of the head and neck who have cancer progression within 6 months after platinum-based chemotherapy administered in the context of primary or recurrent disease have a median survival of 6 months or less.⁵ No therapeutic options prolong survival among these patients.^{5,6}

The recurrence and metastasis of squamous-cell carcinoma of the head and neck are facilitated by immune evasion,⁷ which is mediated in part by expression of the programmed death ligands (PD-L1 and PD-L2) of the T-cell-suppressive immune-checkpoint receptor programmed death 1 (PD-1).⁸⁻¹¹ Nivolumab, a fully human IgG4 anti-PD-1 monoclonal antibody, has shown antitumor efficacy in multiple tumor types.^{12,13} We designed a randomized trial to investigate whether overall survival would be longer with nivolumab therapy than with standard therapy, among patients with platinum-refractory squamous-cell carcinoma of the head and neck.

METHODS

PATIENTS

Eligible patients had histologically confirmed, recurrent squamous-cell carcinoma of the head and neck (including metastatic disease) of the oral cavity, pharynx, or larynx that was not amenable to curative treatment; tumor progression or recurrence within 6 months after the last dose of platinum-containing chemotherapy administered as adjuvant therapy or in the context of primary or recurrent disease; an age of at least 18 years; an Eastern Cooperative Oncology Group performance-status score of 0 or 1 (on a scale from 0 to 5, with higher numbers indicating greater disability); adequate bone marrow, hepatic, and renal function; and measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1.¹⁴ Major exclusion criteria were active brain metastases, autoimmune disease, or systemic immunosuppression; known human immunodeficiency virus or hepatitis B or C virus infection; and previous therapy targeting T-cell costimulating or immune-checkpoint pathways.

TRIAL DESIGN AND TREATMENTS

Patients were randomly assigned in a 2:1 ratio to receive intravenous nivolumab (Opdivo, Bristol-Myers Squibb) or a standard, single-agent therapy of the investigator's choice, with stratification according to receipt of previous cetuximab therapy (yes or no). Nivolumab was administered at a dose of 3 mg per kilogram of body weight every 2 weeks. Standard therapy consisted of weekly intravenous administration of methotrexate at a dose of 40 to 60 mg per square meter of body-surface area, docetaxel at a dose of 30 to 40 mg per square meter, or cetuximab at a dose of 250 mg per square meter after a loading dose of 400 mg per square meter.

END POINTS AND ASSESSMENTS

The primary end point was overall survival, which was defined as the time from randomization to the date of death from any cause. Secondary end points were progression-free survival (time from randomization to the date of disease progression or death) and the rate of objective response according to RECIST, version 1.1. Additional prespecified end points included the time to response; associations between PD-L1 level and human papillomavirus (HPV) status and overall survival, progression-free survival, and response rate; safety; and quality-of-life assessments.

Tumor response was assessed by investigators according to RECIST, version 1.1, every 6 weeks beginning at week 9. Patients were treated until an unacceptable level of drug-related toxic effects occurred or until disease progression. However, nivolumab treatment could be continued beyond disease progression, as assessed clinically or radiographically, if the investigator assessed that it was providing clinical benefit. Patients were followed for overall survival every 3 months until death, loss to follow-up, or withdrawal of consent.

At each treatment visit and for 100 days after receipt of the last dose, acute toxic effects were evaluated according to the Common Terminology Criteria for Adverse Events, version 4.0. Adverse events with potential immunologic causes were classified as select adverse events. The criteria for a dose delay or the discontinuation of nivolumab or standard therapy because of treatment-related adverse events were specified in the protocol, available with the full text of this article at NEJM.org. Dose modifications were not permitted for nivolumab but were specified for metho-

trexate, docetaxel, and cetuximab on the basis of the type and grade of the toxic effect.

Patient-reported outcomes, including symptoms and health-related quality of life, were exploratory end points and were evaluated with the use of the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire–Core 30 module (QLQ-C30) and the head-and-neck–specific module (QLQ-H&N35). Scores for these modules range from 0 to 100, with higher scores indicating better functioning or well-being or higher symptom burden, although scales measuring symptom burden were reverse-scored to facilitate presentation. The proportion of patients reporting health problems was assessed with the use of the three-level version of the European Quality of Life–5 Dimensions (EQ-5D-3L) questionnaire. Patients also completed the EQ-5D-3L visual-analogue scale, for which scores range from 0 to 100 and higher scores indicate better perceived health status.

BIOMARKER ANALYSIS

Fresh or archived pretreatment tumor specimens were obtained after the last therapy and before trial entry from 90.6% of the patients. For patients with oropharyngeal cancer, tumor HPV status, assessed by means of p16 immunohistochemical testing, was required to be documented by local or central analysis and was defined as positive if diffuse staining was present in at least 70% of the tumor cells.¹⁵ Immunochemical testing for p16 was not performed for nonoropharyngeal cancers because of the low prevalence of HPV-positive tumors and poor specificity for HPV status at these anatomical sites.¹⁶ Tumor PD-L1 membrane expression was evaluated centrally by means of immunohistochemical testing (Dako North America) with the use of a rabbit anti-human PD-L1 antibody (clone 28–8, Epitomics) and was scored at prespecified expression levels, including levels of 1% or more, 5% or more, and 10% or more in a minimum of 100 tumor cells that could be evaluated.¹⁷

TRIAL OVERSIGHT

This trial was registered with the National Cancer Institute and was approved by the institutional review board at each participating institution. Written informed consent was obtained from all the patients before enrollment. The trial was designed by the academic authors in collabo-

ration with the sponsor (Bristol-Myers Squibb). The first and last authors attest to the accuracy and completeness of the data and analyses and vouch for adherence of the trial to the protocol. Medical-writing support, funded by the sponsor, was provided by inScience Communications and Chrysalis Medical Communications.

STATISTICAL ANALYSIS

We calculated the required number of events assuming one planned interim analysis of overall survival after 70% of the events occurred and stopping boundaries that were based on an O'Brien–Fleming alpha-spending function.¹⁸ We calculated that a sample of 360 patients and a total of 278 deaths would be required to ensure that a two-sided test procedure with one interim analysis, a 2:1 ratio for randomization, and an experiment-wide false positive rate of 5% would provide the trial with 90% power to detect a hazard ratio of 0.667 for the comparison of nivolumab with standard therapy.

Analyses of baseline characteristics and efficacy followed the intention-to-treat principle. Analyses of dosing and safety were restricted to patients who received at least one dose of therapy. The distributions of overall survival and progression-free survival were estimated by the Kaplan–Meier method and compared by means of log-rank tests stratified according to previous receipt of cetuximab (yes or no). Cox proportional-hazards models (stratified according to status with respect to previous receipt of cetuximab) were used to estimate hazard ratios and compute confidence intervals. A generalization of the Brookmeyer and Crowley method was used to compute confidence intervals for the median survival times, and the Borgan and Liestøl method was used to compute confidence intervals for survival at specific time points.¹⁹

A confidence interval of 97.73% was used for the hazard ratio for death in the analysis of overall survival to reflect the significance level for the interim comparison of overall survival. All other confidence intervals were calculated at the 95% level. The stratum-adjusted Cochran–Mantel–Haenszel method was used to compute the odds ratio and the associated confidence interval for tumor response. The protocol specified that if nivolumab was shown to be superior to standard therapy with respect to overall survival, then progression-free survival and response

rate would each be tested, hierarchically at an alpha level of 5%, to ensure a false positive rate of no more than 5% for testing all three end points.

Prespecified analyses were performed to assess the consistency of treatment effect on the end points in a range of baseline subgroups, including subgroups defined according to PD-L1 expression status and p16 status. A post hoc analysis of treatment effect in PD-L1 expression subgroups ($\geq 1\%$ vs. $< 1\%$) according to p16 status (positive vs. negative) was also performed. In addition, tests for interactions between treatment and PD-L1 expression level (prespecified) and between treatment and p16 status (post hoc) were performed. All these analyses were exploratory and descriptive: no adjustments for multiple comparisons were made, nor was the trial powered to detect interactions.

For patient-reported outcomes, a clinically meaningful change in score was regarded as 10 points for the EORTC QLQ-C30 and QLQ-H&N35 and as 7 points for the visual-analogue scale of the EQ-5D-3L questionnaire.²⁰⁻²² Analysis of covariance was used to compare the mean score changes between groups, with a separate analysis being performed for each patient-reported outcome. Each analysis was adjusted for treatment, visit, status with respect to previous cetuximab use, and the baseline value of the patient-reported outcome.

The data cutoff point for the analyses of overall survival, progression-free survival, and safety was December 18, 2015, which was the date of the planned interim analysis. Data on rate of response were based on a database lock on May 5, 2016. At the interim analysis, the independent data monitoring committee confirmed that the P value for the comparison of overall survival was below the formal statistical boundary for significance of 0.0227.

RESULTS

PATIENTS AND TREATMENT

From June 2014 through August 2015, we randomly assigned 240 patients to receive nivolumab and 121 to receive standard therapy (Fig. S1 in the Supplementary Appendix, available at NEJM.org). Previous treatment included radiotherapy in 91.4% of the patients and two or more lines of systemic therapy in 54.5%. The treat-

ment groups were balanced with respect to most demographic and clinical characteristics (Table 1), although the standard-therapy group included higher percentages of patients 65 years of age or older and of patients who had never smoked. Tumor p16 status was reported, per protocol, for 178 patients (113 patients in the nivolumab group and 65 in the standard-therapy group), and 26.2% of the patients in the nivolumab group and 24.0% in the standard-therapy group had positive p16 status.

Of 361 patients who underwent randomization, 347 (96.1%) received one or more doses of assigned therapy (236 patients in the nivolumab group and 111 in the standard-therapy group). Standard therapies that were administered included methotrexate (in 46 patients), docetaxel (in 52), and cetuximab (in 13). The median duration of treatment was 1.9 months in each group. Data on dose delays and reductions according to treatment group are provided in Table S1 in the Supplementary Appendix. At the time of analysis, 41 of 236 patients (17.4%) were still receiving nivolumab and 3 of 111 (2.7%) were still receiving standard therapy.

EFFICACY

Among 361 patients who underwent randomization, 133 deaths (55.4% of patients) occurred in the nivolumab group and 85 deaths (70.2% of patients) occurred in the standard-therapy group. The median duration of follow-up for overall survival was 5.1 months (range, 0 to 16.8).

The median overall survival was 7.5 months (95% confidence interval [CI], 5.5 to 9.1) in the nivolumab group versus 5.1 months (95% CI, 4.0 to 6.0) in the standard-therapy group. Overall survival was significantly longer with nivolumab than with standard therapy, and nivolumab-treated patients had a risk of death that was 30% lower than the risk among patients assigned to standard therapy (hazard ratio, 0.70; 97.73% CI, 0.51 to 0.96; $P=0.01$) (Fig. 1A). The delayed separation of the Kaplan–Meier curves for overall survival is indicative of nonproportionality, and the hazard ratio should be thought of as an average over time.²³ The estimated rate of overall survival at 1 year among patients treated with nivolumab (36.0%; 95% CI, 28.5 to 43.4) was more than double the rate with standard therapy (16.6%; 95% CI, 8.6 to 26.8).

Nivolumab was associated with longer median

Characteristic	Nivolumab (N=240)	Standard Therapy (N=121)	Total (N=361)
Age			
Median (range) — yr	59 (29–83)	61 (28–78)	60 (28–83)
≥75 yr — no. (%)	12 (5.0)	6 (5.0)	18 (5.0)
Male sex — no. (%)	197 (82.1)	103 (85.1)	300 (83.1)
Race — no. (%)†			
White	196 (81.7)	104 (86.0)	300 (83.1)
Asian	29 (12.1)	14 (11.6)	43 (11.9)
Black	10 (4.2)	3 (2.5)	13 (3.6)
Other	5 (2.1)	0	5 (1.4)
Smoking or tobacco use — no. (%)			
Current or former	191 (79.6)	85 (70.2)	276 (76.5)
Never	39 (16.2)	31 (25.6)	70 (19.4)
Not reported	10 (4.2)	5 (4.1)	15 (4.2)
ECOG performance-status score — no. (%)‡			
0	49 (20.4)	23 (19.0)	72 (19.9)
1	189 (78.8)	94 (77.7)	283 (78.4)
≥2	1 (0.4)	3 (2.5)	4 (1.1)
Not reported	1 (0.4)	1 (0.8)	2 (0.6)
Site of primary tumor — no. (%)			
Larynx	34 (14.2)	15 (12.4)	49 (13.6)
Oral cavity	108 (45.0)	67 (55.4)	175 (48.5)
Pharynx	92 (38.3)	36 (29.8)	128 (35.5)
Other§	6 (2.5)	3 (2.5)	9 (2.5)
No. of previous lines of systemic cancer therapy — no. (%)¶			
1	106 (44.2)	58 (47.9)	164 (45.4)
2	80 (33.3)	45 (37.2)	125 (34.6)
≥3	54 (22.5)	18 (14.9)	72 (19.9)
Context of previous systemic therapy regimen — no. (%) 			
Adjuvant therapy	37 (15.4)	21 (17.4)	58 (16.1)
Neoadjuvant therapy	17 (7.1)	16 (13.2)	33 (9.1)
Primary disease	173 (72.1)	83 (68.6)	256 (70.9)
Metastatic disease	112 (46.7)	59 (48.8)	171 (47.4)
Previous receipt of cetuximab — no. (%)	150 (62.5)	72 (59.5)	222 (61.5)

* There were no significant ($P<0.05$) between-group differences in the characteristics listed here, except for smoking ($P=0.047$). Percentages may not total 100 because of rounding.

† Race was self-reported.

‡ Eastern Cooperative Oncology Group (ECOG) performance status is scored on a scale from 0 to 5, with higher numbers indicating greater disability.

§ The "Other" category included patients with a tumor in more than one of the categories (i.e., larynx, oral cavity, or pharynx).

¶ A line of systemic chemotherapy was defined as any chemotherapy that was administered as part of primary therapy for squamous-cell carcinoma of the head and neck (e.g., induction or concurrent chemoradiotherapy) or any single-agent or multiple-agent chemotherapy regimen that was administered after a diagnosis of recurrent squamous-cell carcinoma of the head and neck.

|| Patients may have received previous systemic therapy in more than one context.

overall survival than all the options for standard therapy: methotrexate (median, 4.6 months; hazard ratio for death, 0.64; 95% CI, 0.43 to 0.96), docetaxel (median, 5.8 months; hazard ratio, 0.82; 95% CI, 0.53 to 1.28), and cetuximab (median, 4.1 months; hazard ratio, 0.47; 95% CI, 0.22 to 1.01). Across prespecified demographic and clinical subgroups, the estimate of the hazard ratio for death in the analysis of overall survival with nivolumab versus standard therapy was less than 1 (Fig. 1C, and Fig. S2 in the Supplementary Appendix).

No significant difference between groups was observed with regard to the rate of progression-free survival (hazard ratio for disease progression or death, 0.89; 95% CI, 0.70 to 1.13; $P=0.32$). The crossing of the Kaplan–Meier curves is indicative of nonproportionality. The median progression-free survival was 2.0 months (95% CI, 1.9 to 2.1) in the nivolumab group versus 2.3 months (95% CI, 1.9 to 3.1) in the standard-therapy group (Fig. 1B). However, a late separation in the Kaplan–Meier curves was observed, and the estimated rates of progression-free survival at 6 months were 19.7% (95% CI, 14.6 to 25.4) in the nivolumab group and 9.9% (95% CI, 5.0 to 16.9) in the standard-therapy group.

The response rate among nivolumab-treated patients was 13.3% (95% CI, 9.3 to 18.3), including 6 complete responses and 26 partial responses. In the standard-therapy group, the response rate was 5.8% (95% CI, 2.4 to 11.6), including 1 complete response and 6 partial responses. The median time to response was 2.1 months with nivolumab versus 2.0 months with standard therapy. Tumor reductions were more durable with nivolumab, as indicated by the tumor-burden plots over time for patients who had either a partial response or a complete response (Fig. S3 in the Supplementary Appendix).

PD-L1 EXPRESSION AND P16 STATUS

A prespecified, exploratory analysis was performed to evaluate the consistency of the treatment effect in subgroups defined according to tumor PD-L1 expression level ($\geq 1\%$ vs. $< 1\%$) (Table 2). Tumor PD-L1 expression status could be evaluated in 260 of 361 patients (72.0%) (Table S2 in the Supplementary Appendix). Among the patients who could be evaluated, 57.3% had a PD-L1 expression level of 1% or more.

In the analysis of overall survival in the sub-

group of patients with a PD-L1 expression level of 1% or more, the hazard ratio for death among patients treated with nivolumab versus standard therapy was 0.55 (95% CI, 0.36 to 0.83) (Fig. 2A), whereas in the subgroup of patients with a PD-L1 expression level of less than 1%, the hazard ratio was 0.89 (95% CI, 0.54 to 1.45; $P=0.17$ for interaction) (Fig. 2B). The estimates of the hazard ratio for death in the analysis of overall survival in the subgroups of patients with PD-L1 expression levels of 5% or more and of 10% or more were similar to those among patients with PD-L1 expression levels of 1% or more (Table 2).

In our post hoc exploratory analysis involving the 178 patients for whom tumor p16 status was reported, the median overall survival appeared to be longer with nivolumab than with standard therapy regardless of p16 status (Table 2). Among patients with p16-positive tumors, the median overall survival was 9.1 months in the nivolumab group versus 4.4 months in the standard-therapy group (hazard ratio for death, 0.56; 95% CI, 0.32 to 0.99); among patients with p16-negative tumors, the median overall survival was 7.5 versus 5.8 months (hazard ratio, 0.73; 95% CI, 0.42 to 1.25; $P=0.55$ for interaction) (Figs. S4 and S5 in the Supplementary Appendix).

We further explored the effect of nivolumab versus standard therapy on overall survival in subgroups defined according to both PD-L1 expression ($\geq 1\%$ vs. $< 1\%$) and tumor p16 status (positive vs. negative) (Table 2). The estimated hazard ratios for death in the analysis of overall survival with nivolumab versus standard therapy were less than 1 in all four subgroups. Results of the exploratory analysis of the treatment effect on response rates in the subgroups defined according to tumor PD-L1 level and p16 status are provided in Table S3 in the Supplementary Appendix.

SAFETY

The most common treatment-related adverse events are shown in Table 3 (see also Tables S4, S5, and S6 in the Supplementary Appendix). The rates of treatment-related adverse events of any grade were similar in the two groups, but fewer events of grade 3 or 4 were reported in the nivolumab group than in the standard-therapy group (occurring in 13.1% vs. 35.1% of patients). In the nivolumab group, the most frequent adverse events of any grade were fatigue, nausea,

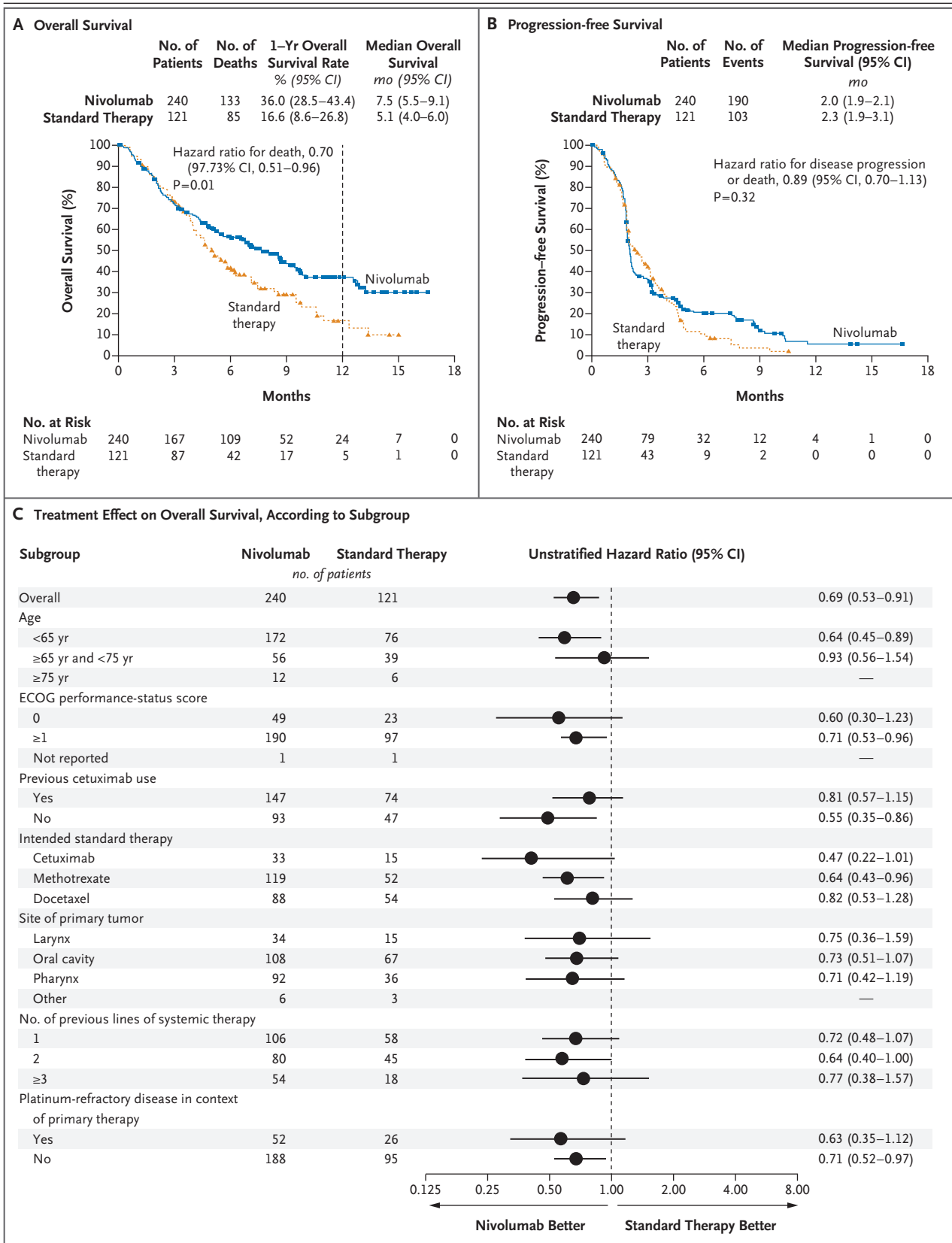


Figure 1 (facing page). Overall Survival, Progression-free Survival, and Treatment Effect on Overall Survival According to Subgroup.

Panel A shows the Kaplan–Meier curves for overall survival among all the patients who underwent randomization and were assigned to receive either nivolumab or standard therapy. In the planned interim analysis, the boundary for statistical significance for overall survival required the P value to be less than 0.0227. Panel B shows the Kaplan–Meier curves for progression-free survival among all the patients who underwent randomization. Symbols indicate censored observations. Hazard ratios (and confidence intervals) were computed with the use of a stratified Cox proportional-hazards model, and the P values were from a stratified log-rank test. Panel C shows a forest plot of unstratified hazard ratios for death in the analysis of the treatment effect according to demographic and clinical subgroups at baseline. Hazard ratios were not calculated for subgroups that included fewer than 20 patients across the two groups. Platinum-refractory disease in the context of primary therapy refers to cancer progression within 6 months after platinum therapy administered in the context of primary or adjuvant therapy (a post hoc derived analysis).

rash, decreased appetite, and pruritus. Among the select adverse events, gastrointestinal events were less common with nivolumab than with standard therapy (occurring in 6.8% vs. 14.4% of the patients; primarily diarrhea), whereas adverse events of the skin were more common with nivolumab (in 15.7% vs. 12.6%; primarily rash and pruritus), as were adverse events of the endo-

crine system (in 7.6% vs. 0.9%; primarily hypothyroidism). Pneumonitis was observed in 2.1% of the patients treated with nivolumab. Two treatment-related deaths were reported in the nivolumab group (pneumonitis and hypercalcemia in one patient each), and one patient in the standard-therapy group died from a treatment-related lung infection.

Table 2. Exploratory Analysis of Overall Survival According to Tumor PD-L1 Expression and p16 Status Subgroups.*

Variable	Nivolumab (N=240)		Standard Therapy (N=121)		Hazard Ratio for Death (95% CI)
	Patients	Median Survival	Patients	Median Survival	
	no. (%)	mo	no. (%)	mo	
All patients	240 (100.0)	7.5	121 (100.0)	5.1	0.69 (0.53–0.91)
PD-L1 expression level					
≥1%	88 (36.7)	8.7	61 (50.4)	4.6	0.55 (0.36–0.83)
≥5%	54 (22.5)	8.8	43 (35.5)	4.6	0.50 (0.30–0.83)
≥10%	43 (17.9)	8.7	34 (28.1)	5.2	0.56 (0.31–1.01)
<1%	73 (30.4)	5.7	38 (31.4)	5.8	0.89 (0.54–1.45)
<5%	107 (44.6)	7.0	56 (46.3)	5.1	0.81 (0.55–1.21)
<10%	118 (49.2)	7.2	65 (53.7)	4.6	0.73 (0.50–1.06)
Not quantifiable	79 (32.9)	7.8	22 (18.2)	5.8	0.79 (0.44–1.44)
p16 status					
Positive	63 (26.2)	9.1	29 (24.0)	4.4	0.56 (0.32–0.99)
Negative	50 (20.8)	7.5	36 (29.8)	5.8	0.73 (0.42–1.25)
Combined subgroup					
PD-L1 ≥1% and p16-positive	23 (9.6)	8.8	14 (11.6)	3.9	0.50 (0.21–1.19)
PD-L1 ≥1% and p16-negative	17 (7.1)	8.8	16 (13.2)	5.6	0.44 (0.18–1.10)
PD-L1 <1% and p16-positive	24 (10.0)	10.0	10 (8.3)	6.4	0.55 (0.22–1.39)
PD-L1 <1% and p16-negative	14 (5.8)	7.1	12 (9.9)	7.4	0.82 (0.31–2.19)

* Expression of the programmed death 1 ligand 1 (PD-L1) was measured in 260 patients (161 patients in the nivolumab group and 99 in the standard-therapy group), and the p16 level in 178 patients (113 in the nivolumab group and 65 in the standard-therapy group). Hazard ratios are from unstratified Cox proportional-hazards models.

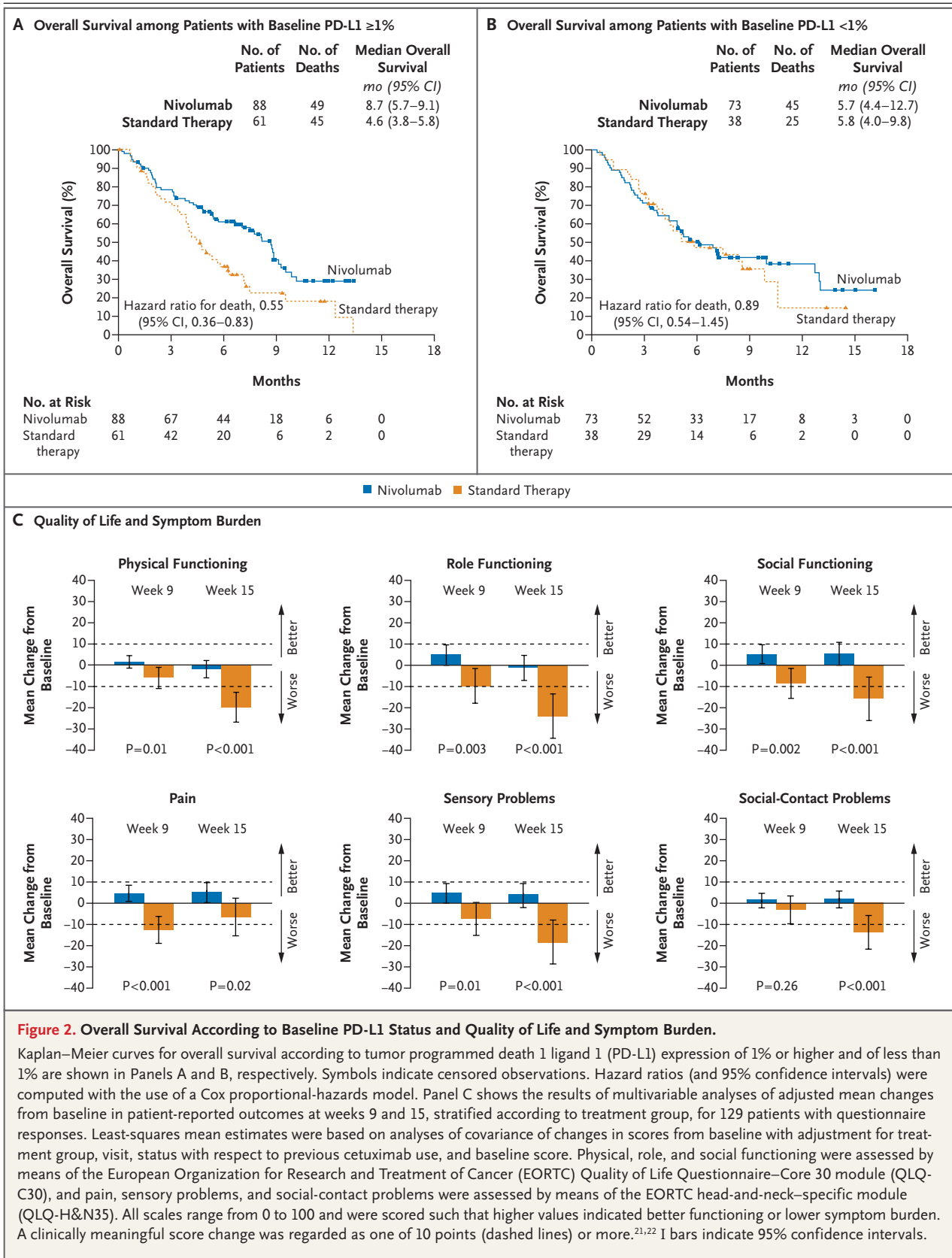


Table 3. Treatment-Related Adverse Events Occurring in at Least 5% of the Patients in Either Group.

Event	Nivolumab (N=236)		Standard Therapy (N=111)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	<i>number of patients (percent)</i>			
Any event	139 (58.9)*	31 (13.1)	86 (77.5)†	39 (35.1)
Fatigue	33 (14.0)	5 (2.1)	19 (17.1)	3 (2.7)
Nausea	20 (8.5)	0	23 (20.7)	1 (0.9)
Rash	18 (7.6)	0	5 (4.5)	1 (0.9)
Decreased appetite	17 (7.2)	0	8 (7.2)	0
Pruritus	17 (7.2)	0	0	0
Diarrhea	16 (6.8)	0	15 (13.5)	2 (1.8)
Anemia	12 (5.1)	3 (1.3)	18 (16.2)	5 (4.5)
Asthenia	10 (4.2)	1 (0.4)	16 (14.4)	2 (1.8)
Vomiting	8 (3.4)	0	8 (7.2)	0
Dry skin	7 (3.0)	0	10 (9.0)	0
Stomatitis	5 (2.1)	1 (0.4)	10 (9.0)	3 (2.7)
Weight loss	4 (1.7)	0	6 (5.4)	0
Mucosal inflammation	3 (1.3)	0	14 (12.6)	2 (1.8)
Peripheral neuropathy	1 (0.4)	0	7 (6.3)	0
Alopecia	0	0	14 (12.6)	3 (2.7)
Neutropenia	0	0	9 (8.1)	8 (7.2)

* Data include one patient with a grade 5 event of hypercalcemia and one patient with grade 3 pneumonitis who subsequently died of a grade 5 pulmonary embolism.

† Data include one patient with a grade 5 event of lung infection.

PATIENT-REPORTED OUTCOMES

Patient-reported quality-of-life measures were similar at baseline among patients randomly assigned to the nivolumab group and those assigned to the standard-therapy group (Table S7 in the Supplementary Appendix). Analyses were limited to data collected through week 15 owing to a low number of responses to the questionnaires in the standard-therapy group after that time point (Table S8 in the Supplementary Appendix). Patients in the standard-therapy group reported clinically meaningful worsening of physical, role, and social functioning (as assessed by means of the QLQ-C30), as well as of pain, sensory problems, and social-contact problems (as assessed by means of the QLQ-H&N35). Conversely, among patients treated with nivolumab, these measures remained nearly stable or showed slight improvements. P values showed significant between-group differences at both week 9 and week 15 for most comparisons (Fig. 2C). Additional patient-reported outcome data, including health problems and evaluations of health as

measured by the EQ-5D-3L questionnaire, are provided in Table S9 in the Supplementary Appendix.

DISCUSSION

Among patients with recurrent squamous-cell carcinoma of the head and neck who had disease progression after platinum-based chemotherapy, treatment with nivolumab resulted in significantly longer survival than treatment with standard therapy. Patients who were treated with nivolumab had stability in several measures of quality of life, whereas the patients who received standard therapy had declines in these measures.

Our exploratory biomarker analysis indicated that patients who were treated with nivolumab appeared to have longer overall survival than those treated with standard therapy, regardless of tumor PD-L1 expression or p16 status. Although we observed preliminary evidence that patients with a tumor PD-L1 expression level of 1% or more or p16-positive tumors (or both) may have

a greater magnitude of effect from nivolumab therapy than those whose PD-L1 level was less than 1% or who had p16-negative tumors, the interactions were not significant and were not corrected for multiple comparisons. The response data from this trial are consistent with those from a previous phase 1b trial of anti-PD-1 therapy.^{24,25}

In conclusion, nivolumab prolonged survival, as compared with standard therapy, among patients with platinum-refractory squamous-cell carcinoma of the head and neck. Nivolumab was associated with fewer toxic effects of grade 3 or 4 than standard therapy (13.1% vs. 35.1%) and with maintenance of quality of life among pa-

tients with a treatment-refractory cancer that otherwise has serious adverse effects on quality of life as it leads to death.

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APPENDIX

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REFERENCES

1. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer* 2015;136(5):E359-86.
2. Pignon JP, le Maître A, Maillard E, Bourhis J. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): an update on 93 randomised trials and 17,346 patients. *Radiother Oncol* 2009;92:4-14.
3. Bernier J, Dommene C, Ozsahin M, et al. Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. *N Engl J Med* 2004;350:1945-52.
4. Cooper JS, Pajak TF, Forastiere AA, et al. Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck. *N Engl J Med* 2004;350:1937-44.
5. Saloura V, Cohen EE, Licitra L, et al. An open-label single-arm, phase II trial of zalutumumab, a human monoclonal anti-EGFR antibody, in patients with platinum-refractory squamous cell carcinoma of the head and neck. *Cancer Chemother Pharmacol* 2014;73:1227-39.
6. Machiels JP, Haddad RI, Fayette J, et al. Afatinib versus methotrexate as second-line treatment in patients with recurrent or metastatic squamous-cell carcinoma of the head and neck progressing on or after platinum-based therapy (LUX-Head & Neck 1): an open-label, randomised phase 3 trial. *Lancet Oncol* 2015;16:583-94.
7. Ferris RL. Immunology and immunotherapy of head and neck cancer. *J Clin Oncol* 2015;33:3293-304.
8. Topalian SL, Drake CG, Pardoll DM. Immune checkpoint blockade: a common denominator approach to cancer therapy. *Cancer Cell* 2015;27:450-61.
9. Li J, Jie HB, Lei Y, et al. PD-1/SHP-2 inhibits Tc1/Th1 phenotypic responses and the activation of T cells in the tumor microenvironment. *Cancer Res* 2015;75:508-18.
10. Badoual C, Hans S, Merillon N, et al. PD-1-expressing tumor-infiltrating T cells are a favorable prognostic biomarker in HPV-associated head and neck cancer. *Cancer Res* 2013;73:128-38.
11. Concha-Benavente F, Srivastava RM, Trivedi S, et al. Identification of the cell-intrinsic and -extrinsic pathways downstream of EGFR and IFN γ that induce PD-L1 expression in head and neck cancer. *Cancer Res* 2016;76:1031-43.
12. Brahmer J, Reckamp KL, Baas P, et al. Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. *N Engl J Med* 2015;373:123-35.
13. Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. *N Engl J Med* 2015;373:1627-39.
14. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* 2009;45:228-47.
15. Jordan RC, Lingen MW, Perez-Ordóñez B, et al. Validation of methods for oropharyngeal cancer HPV status determination in US cooperative group trials. *Am J Surg Pathol* 2012;36:945-54.
16. Castellsagué X, Alemany L, Quer M, et al. HPV involvement in head and neck cancers: comprehensive assessment of biomarkers in 3680 patients. *J Natl Cancer Inst* 2016 January 28 (Epub ahead of print).
17. Cogswell JP, Goldberg SM, Gupta AK, Jure-Kunkel M, Wang XT, Wigginton JM. Cancer immunotherapy by disrupting PD-1/PD-L1 signaling. *FreePatentsOnline*

- .com. November 21, 2013 (<http://www.freepatentsonline.com/20130309250.pdf>).
18. O'Brien PC, Fleming TR. A multiple testing procedure for clinical trials. *Biometrics* 1979;35:549-56.
19. Klein JP, Moeschberger ML. *Survival analysis: techniques for censored and truncated data*. New York: Springer-Verlag, 1997.
20. Pickard AS, Neary MP, Cella D. Estimation of minimally important differences in EQ-5D utility and VAS scores in cancer. *Health Qual Life Outcomes* 2007; 5:70.
21. Osoba D, Rodrigues G, Myles J, Zee B, Pater J. Interpreting the significance of changes in health-related quality-of-life scores. *J Clin Oncol* 1998;16:139-44.
22. Bottomley A, Tridello G, Coens C, et al. An international phase 3 trial in head and neck cancer: quality of life and symptom results: EORTC 24954 on behalf of the EORTC Head and Neck and the EORTC Radiation Oncology Group. *Cancer* 2014; 120:390-8.
23. Allison PD. *Survival analysis using SAS: a practical guide*. Cary, NC: SAS Institute, 1995.
24. Seiwert TY, Burtneß B, Mehra R, et al. Safety and clinical activity of pembrolizumab for treatment of recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-012): an open-label, multicentre, phase 1b trial. *Lancet Oncol* 2016;17:956-65.
25. Mehra R, Seiwert TY, Mahipal A, et al. Efficacy and safety of pembrolizumab in recurrent/metastatic head and neck squamous cell carcinoma (R/M HNSCC): pooled analyses after long-term follow-up in KEYNOTE-012. Presented at the American Society of Clinical Oncology Annual Meeting, Chicago, June 3-7, 2016. abstract.

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