ORIGINAL ARTICLE

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

R.L. Ferris, G. Blumenschein, Jr., J. Fayette, J. Guigay, A.D. Colevas, L. Licitra, K. Harrington, S. Kasper, E.E. Vokes, C. Even, F. Worden, N.F. Saba, L.C. Iglesias Docampo, R. Haddad, T. Rordorf, N. Kiyota, M. Tahara, M. Monga, M. Lynch, W.J. Geese, J. Kopit, J.W. Shaw, and M.L. Gillison

## 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.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Gillison at the Ohio State University Comprehensive Cancer Center, Ohio State University, 420 W. 12th Ave., Rm. 690, Columbus, OH 43210, or at maura.gillison@osumc.edu.

Drs. Ferris and Gillison contributed equally to this article.

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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 antihuman 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 collaboration 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 (≥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 treatment 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

**Table 1. Characteristics at Baseline and Previous Therapy.***

| 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 (≥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 subgroup 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).

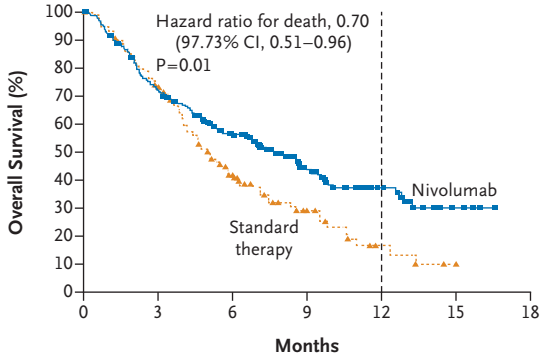
We further explored the effect of nivolumab versus standard therapy on overall survival in subgroups defined according to both PD-L1 expression (≥1% vs. <1%) and tumor p16 status (positive vs. negative) (Table 2). The estimated hazard ratios for death in the analysis of overall survival with nivolumab 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,

**A Overall Survival**

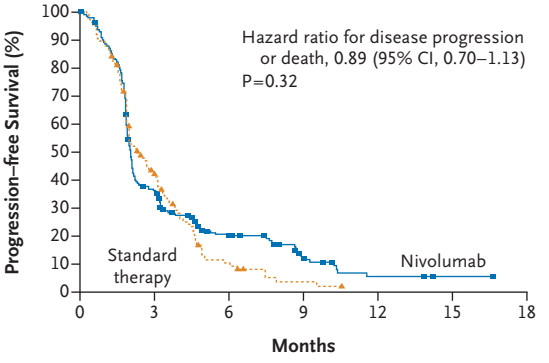
| | No. of Patients | No. of Deaths | 1–Yr Overall Survival Rate % (95% CI) | Median Overall Survival mo (95% CI) |
|---|---|---|---|---|
| Nivolumab | 240 | 133 | 36.0 (28.5–43.4) | 7.5 (5.5–9.1) |
| Standard Therapy | 121 | 85 | 16.6 (8.6–26.8) | 5.1 (4.0–6.0) |




| No. at Risk | | | | | | | |
|---|---|---|---|---|---|---|---|
| Nivolumab | 240 | 167 | 109 | 52 | 24 | 7 | 0 |
| Standard therapy | 121 | 87 | 42 | 17 | 5 | 1 | 0 |

**B Progression-free Survival**

| | No. of Patients | No. of Events | Median Progression-free Survival (95% CI) mo |
|---|---|---|---|
| Nivolumab | 240 | 190 | 2.0 (1.9–2.1) |
| Standard Therapy | 121 | 103 | 2.3 (1.9–3.1) |




| No. at Risk | | | | | | | |
|---|---|---|---|---|---|---|---|
| Nivolumab | 240 | 79 | 32 | 12 | 4 | 1 | 0 |
| Standard therapy | 121 | 43 | 9 | 2 | 0 | 0 | 0 |

**C Treatment Effect on Overall Survival, According to Subgroup**

| Subgroup | Nivolumab (no. of patients) | Standard Therapy (no. of patients) | Unstratified Hazard Ratio (95% CI) |
|---|---|---|---|
| Overall | 240 | 121 | 0.69 (0.53–0.91) |
| Age | | | |
| <65 yr | 172 | 76 | 0.64 (0.45–0.89) |
| ≥65 yr and <75 yr | 56 | 39 | 0.93 (0.56–1.54) |
| ≥75 yr | 12 | 6 | — |
| ECOG performance-status score | | | |
| 0 | 49 | 23 | 0.60 (0.30–1.23) |
| ≥1 | 190 | 97 | 0.71 (0.53–0.96) |
| Not reported | 1 | 1 | — |
| Previous cetuximab use | | | |
| Yes | 147 | 74 | 0.81 (0.57–1.15) |
| No | 93 | 47 | 0.55 (0.35–0.86) |
| Intended standard therapy | | | |
| Cetuximab | 33 | 15 | 0.47 (0.22–1.01) |
| Methotrexate | 119 | 52 | 0.64 (0.43–0.96) |
| Docetaxel | 88 | 54 | 0.82 (0.53–1.28) |
| Site of primary tumor | | | |
| Larynx | 34 | 15 | 0.75 (0.36–1.59) |
| Oral cavity | 108 | 67 | 0.73 (0.51–1.07) |
| Pharynx | 92 | 36 | 0.71 (0.42–1.19) |
| Other | 6 | 3 | — |
| No. of previous lines of systemic therapy | | | |
| 1 | 106 | 58 | 0.72 (0.48–1.07) |
| 2 | 80 | 45 | 0.64 (0.40–1.00) |
| ≥3 | 54 | 18 | 0.77 (0.38–1.57) |
| Platinum-refractory disease in context of primary therapy | | | |
| Yes | 52 | 26 | 0.63 (0.35–1.12) |
| No | 188 | 95 | 0.71 (0.52–0.97) |

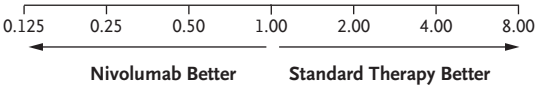


**Figure 1 (facing page). Overall Survival, Progression-free Survival, and Treatment Effect on Overall Survival According to Subgroup.**

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 endocrine 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.

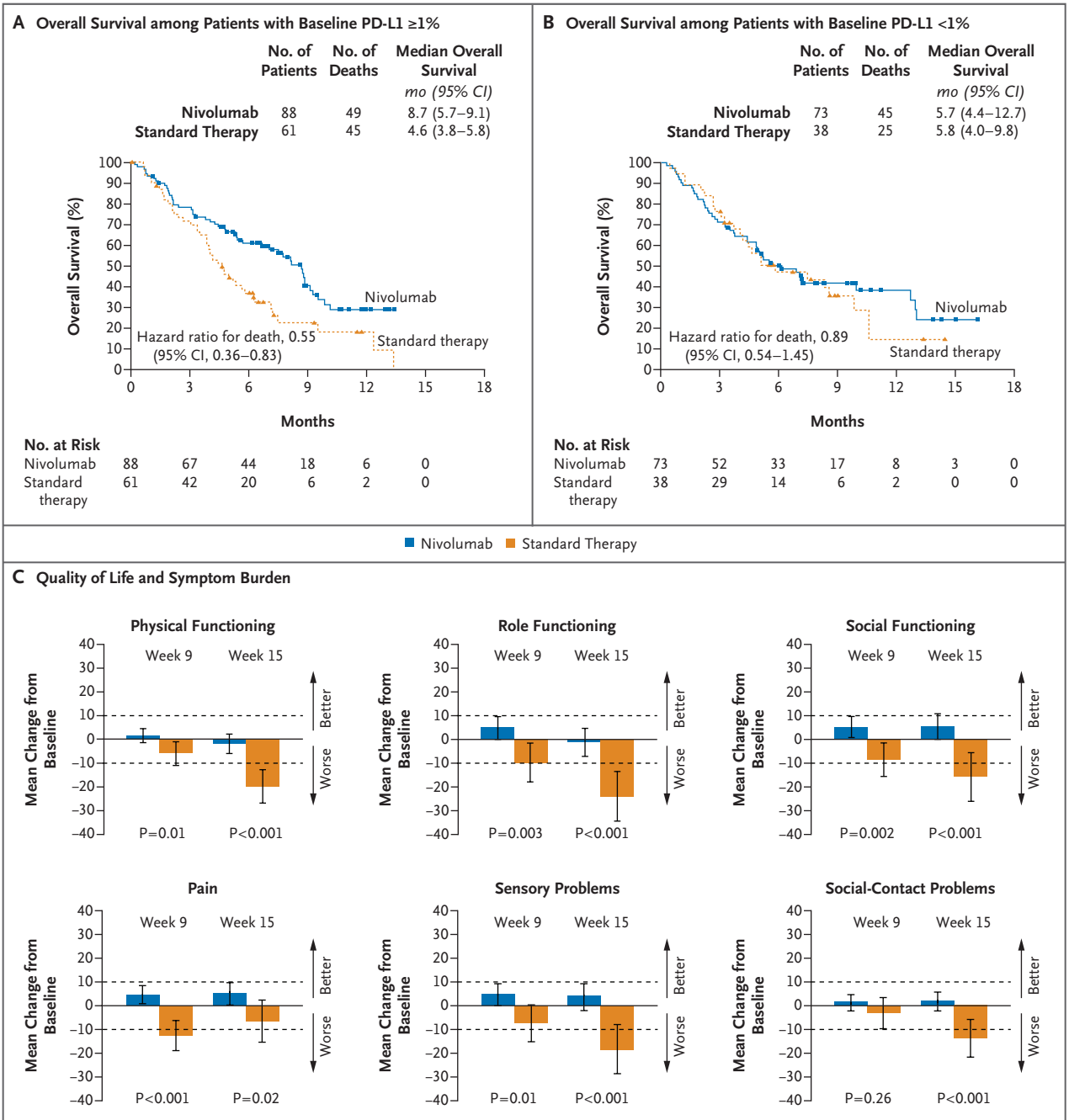



**Figure 2. Overall Survival According to Baseline PD-L1 Status and Quality of Life and Symptom Burden.**

Kaplan–Meier curves for overall survival according to tumor programmed death 1 ligand 1 (PD-L1) expression of 1% or higher and of less than 1% are shown in Panels A and B, respectively. Symbols indicate censored observations. Hazard ratios (and 95% confidence intervals) were computed with the use of a Cox proportional-hazards model. Panel C shows the results of multivariable analyses of adjusted mean changes from baseline in patient-reported outcomes at weeks 9 and 15, stratified according to treatment group, for 129 patients with questionnaire responses. Least-squares mean estimates were based on analyses of covariance of changes in scores from baseline with adjustment for treatment group, visit, status with respect to previous cetuximab use, and baseline score. Physical, role, and social functioning were assessed by means of the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire–Core 30 module (QLQ-C30), and pain, sensory problems, and social-contact problems were assessed by means of the EORTC head-and-neck–specific module (QLQ-H&N35). All scales range from 0 to 100 and were scored such that higher values indicated better functioning or lower symptom burden. A clinically meaningful score change was regarded as one of 10 points (dashed lines) or more.[21,22] I bars indicate 95% confidence intervals.

**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 |
| | *number of patients (percent)* | | | |
| 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 patients 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

The authors' full names and academic degrees are as follows: Robert L. Ferris, M.D., Ph.D., George Blumenschein, Jr., M.D., Jerome Fayette, M.D., Ph.D., Joel Guigay, M.D., A. Dimitrios Colevas, M.D., Lisa Licitra, M.D., Kevin Harrington, Ph.D., F.R.C.P., F.R.C.R., Stefan Kasper, M.D., Everett E. Vokes, M.D., Caroline Even, M.D., Francis Worden, M.D., Nabil F. Saba, M.D., Lara C. Iglesias Docampo, M.D., Robert Haddad, M.D., Tamara Rordorf, M.D., Naomi Kiyota, M.D., Ph.D., Makoto Tahara, M.D., Ph.D., Manish Monga, M.D., Mark Lynch, Ph.D., William J. Geese, Ph.D., Justin Kopit, Ph.D., James W. Shaw, Pharm.D., Ph.D., M.P.H., and Maura L. Gillison, M.D., Ph.D.

The authors' affiliations are as follows: the University of Pittsburgh Medical Center and Cancer Institute, Pittsburgh (R.L.F.); the Department of Thoracic–Head and Neck Medical Oncology, University of Texas M.D. Anderson Cancer Center, Houston (G.B.); Centre Leon Berard, Lyon (J.F.), Centre Antoine Lacassagne, Nice (J.G.), and Institut Gustave Roussy, Villejuif (C.E.) — all in France; Stanford Cancer Institute, Stanford, CA (A.D.C.); Fondazione Istituto di Ricovero e Cura a Carattere Scientifico, Istituto Nazionale Tumori, Milan (L.L.); Institute of Cancer Research–Royal Marsden National Institute for Health Research Biomedical Research Centre, London (K.H.); University Hospital Essen, Essen, Germany (S.K.); University of Chicago, Chicago (E.E.V.); University of Michigan, Ann Arbor (F.W.); Winship Cancer Institute of Emory University, Atlanta (N.F.S.); Hospital Universitario 12 de Octubre, Madrid (L.C.I.D.); Dana–Farber Cancer Institute, Boston (R.H.); Universitätsspital Zurich, Zurich, Switzerland (T.R.); Kobe University Hospital, Kobe (N.K.), and National Cancer Center Hospital East, Kashiwa (M.T.) — both in Japan; Bristol-Myers Squibb, Princeton, NJ (M.M., M.L., W.J.G., J.K., J.W.S.); and Ohio State University, Columbus (M.L.G.).

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