ORIGINAL ARTICLE

# Neoadjuvant and Adjuvant Pembrolizumab in Locally Advanced Head and Neck Cancer

R. Uppaluri,[1,2] R.I. Haddad,[1,2] Y. Tao,[3] C. Le Tourneau,[4] N.Y. Lee,[5] W. Westra,[6] R. Chernock,[7] M. Tahara,[8] K.J. Harrington,[9] A.L. Klochikhin,[10] I. Braña,[11] G. Vasconcelos Alves,[12] B.G.M. Hughes,[13] M. Oliva,[14] I. Pinto Figueiredo Lima,[15] T. Ueda,[16] T. Rutkowski,[17] U. Schroeder,[18] P.-S. Mauz,[19] T. Fuereder,[20] S. Laban,[21] N. Oridate,[22] A. Popovtzer,[23] N. Mach,[24] Y. Korobko,[25] D.A. Costa,[26] A. Hooda-Nehra,[27,28] C.P. Rodriguez,[29] R.B. Bell,[30] C. Manschot,[31] K. Benjamin,[31] B. Gumuscu,[31] and D. Adkins,[32] for the KEYNOTE-689 Investigators*

## ABSTRACT

### BACKGROUND

The benefit of the addition of perioperative pembrolizumab to standard care with surgery and adjuvant therapy for patients with locally advanced head and neck squamous-cell carcinoma (HNSCC) is unclear.

### METHODS

In this phase 3, open-label trial, we randomly assigned participants with locally advanced HNSCC in a 1:1 ratio to receive 2 cycles of neoadjuvant pembrolizumab and 15 cycles of adjuvant pembrolizumab (both at a dose of 200 mg every 3 weeks) in addition to standard care (pembrolizumab group) or standard care alone (control group). Standard care was surgery and adjuvant radiotherapy with or without concomitant cisplatin. The primary end point was event-free survival, sequentially assessed in participants whose tumors expressed programmed death ligand 1 (PD-L1) with a combined positive score (CPS) of 10 or more (CPS-10 population), participants whose tumors expressed PD-L1 with a CPS of 1 or more (CPS-1 population), and all the participants. A higher CPS indicates a higher proportion of cells that express PD-L1.

### RESULTS

A total of 363 participants (234 with a CPS of ≥10 and 347 with a CPS of ≥1) were assigned to the pembrolizumab group and 351 (231 with a CPS of ≥10 and 335 with a CPS of ≥1) to the control group. Surgery was completed in approximately 88% of the participants in each group. At the first interim analysis, the median follow-up was 38.3 months. Event-free survival at 36 months was 59.8% in the pembrolizumab group and 45.9% in the control group (hazard ratio for progression, recurrence, or death, 0.66; 95% confidence interval [CI], 0.49 to 0.88; two-sided P=0.004) in the CPS-10 population; 58.2% and 44.9%, respectively (hazard ratio, 0.70; 95% CI, 0.55 to 0.89; two-sided P=0.003), in the CPS-1 population; and 57.6% and 46.4%, respectively (hazard ratio, 0.73; 95% CI, 0.58 to 0.92; two-sided P=0.008), in the total population. Grade 3 or higher treatment-related adverse events occurred in 44.6% of the participants in the pembrolizumab group and in 42.9% of those in the control group, including death in 1.1% and 0.3%, respectively. Potentially immune-mediated adverse events of grade 3 or higher occurred in 10.0% of the participants in the pembrolizumab group.

### CONCLUSIONS

The addition of neoadjuvant and adjuvant pembrolizumab to standard care significantly improved event-free survival among participants with locally advanced HNSCC. Neoadjuvant pembrolizumab did not affect the likelihood of surgical completion. No new safety signals were identified. (Funded by Merck Sharp and Dohme, a subsidiary of Merck [Rahway, NJ]; KEYNOTE-689 ClinicalTrials.gov number, NCT03765918.)

The authors' full names, academic degrees, and affiliations are listed at the end of the article. Dr. Uppaluri can be contacted at ravindra_uppaluri@dfci.harvard.edu or at Brigham and Women's Hospital, 75 Francis St., Boston, MA 02115.

*A complete list of the principal investigators in the KEYNOTE-689 trial is provided in the Supplementary Appendix, available at NEJM.org.

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Resectable locally advanced head and neck squamous-cell carcinoma (HNSCC) is a burdensome disease with few treatment advances in recent decades. Adjuvant radiotherapy remains the standard of care for patients with locally advanced HNSCC without adverse pathological features (e.g., positive margins or extranodal extension).[1,2] Two phase 3 trials, European Organization for Research and Treatment of Cancer (EORTC) 22931 and Radiation Therapy Oncology Group (RTOG) 9501, established radiotherapy with concomitant cisplatin after surgery as the standard of care for high-risk locally advanced HNSCC.[1-4] Nevertheless, approximately a third of patients have disease relapse within 1 year, and less than half are likely to survive to 5 years.[3-6]

Pembrolizumab, an anti–programmed death 1 (PD-1) monoclonal antibody, is a cornerstone of first-line standard care for recurrent and metastatic HNSCC.[1,2,7] The addition of pembrolizumab to established neoadjuvant and adjuvant regimens led to significant improvement in efficacy outcomes in phase 3 trials across multiple tumor types, including lung, breast, and cervical cancers, and renal-cell carcinoma.[8-12] Two phase 2 studies involving patients with locally advanced HNSCC indicated that adding perioperative pembrolizumab to standard care was associated with lower relapse rates and better disease-free survival than historical controls.[13-15] This phase 3, open-label, randomized trial (KEYNOTE-689) investigated the efficacy and safety of neoadjuvant and adjuvant pembrolizumab plus standard care as compared with standard care alone in patients with resectable locally advanced HNSCC.

## Methods

### Participants

Eligible participants were 18 years of age or older and had newly diagnosed, nonmetastatic, resectable locally advanced HNSCC with stage III oropharyngeal p16-positive disease with tumor size T4 and node stage N0 to N2, or stage III or IVA oropharyngeal p16-negative disease, or stage III or IVA laryngeal, hypopharyngeal, or oral cavity disease independent of p16 status. Participants had 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), were eligible for primary surgery, and provided newly obtained tumor tissue for programmed death ligand 1 (PD-L1) and human papillomavirus (HPV) analysis. All the participants provided written informed consent. Complete eligibility criteria are provided in the protocol (available with the full text of this article at NEJM.org).

### Trial Design and Treatments

KEYNOTE-689 is a phase 3, multicenter, open-label, randomized, active-controlled trial conducted at 192 sites across three geographic regions. Participants were randomly assigned in a 1:1 ratio to receive neoadjuvant and adjuvant pembrolizumab in addition to standard care (pembrolizumab group) or to receive standard care alone (control group). Standard care was surgery and adjuvant radiotherapy with or without concomitant cisplatin. Randomization was performed centrally with the use of an interactive voice-response system, with stratification according to primary tumor site (oropharynx or oral cavity vs. larynx vs. hypopharynx), tumor stage (III vs. IVA), and PD-L1 status according to centrally determined tumor proportion score (TPS; ≥50% vs. <50%).

Participants in the pembrolizumab group were planned to receive 2 cycles of intravenous neoadjuvant pembrolizumab (200 mg) every 3 weeks. Participants were planned to undergo surgery within 6 weeks after randomization in the pembrolizumab group and within 4 weeks after randomization in the control group. High risk for recurrence after surgery was defined in the protocol as the presence of positive margins (<1 mm) or extranodal extension, assessed both locally and centrally. According to the protocol, planned postoperative treatment based on risk assessment guided by pathological findings consisted of radiotherapy alone at a dose of 2 Gy per fraction daily in 30 fractions (60 Gy total) for low-risk disease (no positive margins or extranodal extension), or concomitant chemoradiotherapy at a dose of 2 Gy per fraction daily in 33 fractions (66 Gy total) plus cisplatin at a dose of 100 mg per square meter of body-surface area every 3 weeks for 3 cycles for high-risk disease. The dose of radiation and the use of cisplatin were ultimately determined by the investigator according to local guidelines. Postoperative radiotherapy or chemoradiotherapy began after adequate recovery from surgery (recommended ≤6 weeks). The pembrolizumab

group was also planned to receive postoperative pembrolizumab at a dose of 200 mg every 3 weeks (3 cycles concomitant with radiotherapy or chemoradiotherapy starting on day 1 of radiotherapy, followed by 12 cycles on an adjuvant basis); no additional therapy was included for the control group. Participants who did not undergo surgery or had gross residual disease after surgery could receive definitive chemoradiotherapy (planned dose, 2 Gy per fraction daily in 35 fractions for a total of 70 Gy plus cisplatin at 100 mg per square meter every 3 weeks for 3 cycles with or without pembrolizumab, on the basis of trial-group assignment). The trial regimen was continued until the occurrence of confirmed disease progression, unacceptable toxic effects, death, or withdrawal of consent.

#### END POINTS AND ASSESSMENTS

The primary end point is event-free survival assessed by blinded independent central review according to Response Evaluation Criteria in Solid Tumors, version 1.1, in participants whose tumors expressed PD-L1 with a combined positive score (CPS) of 10 or more (CPS-10 population), participants whose tumors expressed PD-L1 with a CPS of 1 or more (CPS-1 population), and all the participants irrespective of the CPS (total population). Event-free survival was defined as the time from randomization to radiographic disease progression occurring during the neoadjuvant phase and preventing surgery, local or distant progression or recurrence on imaging or biopsy, or death from any cause. The CPS was defined as the number of PD-L1–staining cells, including tumor cells, lymphocytes, and macrophages, divided by the total number of viable tumor cells, multiplied by 100.

Key secondary end points are major pathological response (≤10% residual viable invasive squamous-cell carcinoma) assessed by blinded independent pathological review and overall survival in the CPS-10 population, the CPS-1 population, and the total population. Other secondary end points include pathological complete response as assessed by blinded independent pathological review and safety and side-effect profile. The relatedness of adverse events to the trial treatment was determined by the investigators. Definitions and detailed assessments are provided in the Supplementary Appendix, available at NEJM.org.

#### TRIAL OVERSIGHT

This trial was designed by a panel of academic advisors and employees of the sponsor (Merck Sharp and Dohme, a subsidiary of Merck [Rahway, NJ]). The protocol and all amendments were approved by the appropriate ethics body at each participating site. The trial was conducted in accordance with Good Clinical Practices. Regular safety and efficacy assessments at prespecified interim analyses were performed by an external, independent data monitoring committee.

The authors vouch for the fidelity of the trial to the protocol and its amendments and for the accuracy and completeness of the data reported. All the authors participated in the writing or critical review and editing of the manuscript and approved the manuscript for submission. A medical writer employed by the sponsor assisted with the first draft.

#### STATISTICAL ANALYSIS

The trial enrolled 714 participants, with 65% having a CPS of 10 or more (planned, 462 participants) and 96% having a CPS of 1 or more (planned, 680 participants). The sample size was planned such that the CPS-10 population would provide the trial with approximately 94.9% power to detect superiority with respect to event-free survival at a one-sided alpha level of 0.025 in the pembrolizumab group, with an underlying hazard ratio of 0.62, and more than 99.9% power to detect an absolute between-group difference of 25 percentage points in major pathological response. The first prespecified interim analysis was planned after 207 events of disease progression, disease recurrence, or death in the CPS-10 population and 9 months after the last participant underwent randomization. The overall type I error rate across the primary and key secondary end points and multiple populations was strongly controlled at a one-sided alpha level of 2.5% with the use of the graphical method of Maurer and Bretz.[16] A sequential testing strategy was used; superiority with respect to event-free survival was tested by means of stratified log-rank test first in the CPS-10 population at a one-sided alpha level of 0.025, then in the CPS-1 population at a one-sided alpha level of 0.025, and finally in the total population at a one-sided alpha level of 0.025 if each preceding null hypothesis was rejected. Bounds were derived with the use of a Lan–DeMets O'Brien–Fleming spending function. On the basis of the prespecified multiplic-

ity adjustment strategy, if all event-free survival null hypotheses were rejected, the alpha level was reallocated to key secondary hypotheses (major pathological response, tested by stratified Miettinen and Nurminen method, one-sided alpha level of 0.0005; overall survival, tested by stratified log-rank test, one-sided alpha level of 0.0245) in the CPS-10 population.

We report data from the first prespecified interim analysis (data-cutoff date, July 25, 2024). One-sided P-value boundaries were 0.01378 in the CPS-10 population, 0.01242 in the CPS-1 population, and 0.01196 in the total population for event-free survival and 0.0005 in each population for major pathological response and 0.0104 for overall survival in the CPS-10 population. The protocol specified reporting of one-sided P values; in accordance with *Journal* policy, two-sided P values are reported.

Analyses were performed with the use of SAS software, version 9.4. The full analysis plan is available in the protocol (section 10).

## RESULTS

### PARTICIPANTS AND TREATMENT

A total of 1044 participants were screened and 714 underwent randomization (363 to the pembrolizumab group and 351 to the control group) from December 2018 through October 2023. After neoadjuvant therapy in the pembrolizumab group, 321 participants (88.4%) completed surgery; in the control group, 308 participants (87.7%) completed surgery. Surgery delays occurred in 38 participants who received neoadjuvant pembrolizumab and 10 participants who did not receive neoadjuvant pembrolizumab (Table S1 in the Supplementary Appendix); the median time from the end of neoadjuvant therapy (if received) or randomization (if no neoadjuvant therapy) to surgery was 3.0 weeks (range, 0.3 to 12.9) and 1.9 weeks (range, 0.3 to 10.4), respectively.

In total, 267 participants in each group (73.6% in the pembrolizumab group and 76.1% in the control group) started postoperative therapy; of them, 46.4% in the pembrolizumab group and 34.8% in the control group started adjuvant therapy within 6 weeks after surgery (82.0% and 76.8%, respectively, within 8 weeks) (Table S2A). Eight additional participants in each group received definitive radiotherapy or radiochemotherapy without surgery. Reasons for treatment discontinuation before adjuvant therapy are shown in Table S2B. Central assessment identified high-risk pathological features in 118 participants (32.5%) in the pembrolizumab group and 156 (44.4%) in the control group and no high-risk features in 196 (54.0%) and 148 (42.2%), respectively; all others had a status of missing. The percentage of participants who received cisplatin was lower in the pembrolizumab group (107 of 275, 38.9%) than in the control group (139 of 275, 50.5%).

At the data-cutoff date, 155 participants in the pembrolizumab group and 261 participants in the control group had completed treatment, and 11 and 0, respectively, were continuing treatment (Fig. S1). The median follow-up (time from randomization to data-cutoff date) was 38.3 months (range, 9.0 to 66.5). The CPS-10 population included 234 participants (64.5%) in the pembrolizumab group and 231 (65.8%) in the control group; the CPS-1 population included 347 (95.6%) and 335 (95.4%), respectively. Less than 5% of all the participants had a CPS of less than 1. Baseline demographic and disease characteristics were balanced between groups in the total population (Table 1), the CPS-10 population (Table S3A), and the CPS-1 population (Table S3B).

**Table 1. Baseline Characteristics of the Total Population.***

| Characteristic | Pembrolizumab (N=363) | Control (N=351) |
|---|---|---|
| Median age (range) — yr | 60.0 (29–82) | 61.0 (22–87) |
| Male sex — no. (%) | 286 (78.8) | 277 (78.9) |
| ECOG performance-status score of 0 — no. (%)† | 199 (54.8) | 209 (59.5) |
| Geographic region — no. (%) | | |
| North America | 64 (17.6) | 49 (14.0) |
| European Union | 138 (38.0) | 145 (41.3) |
| Rest of the world | 161 (44.4) | 157 (44.7) |

**Table 1. (Continued.)**

| Characteristic | Pembrolizumab (N=363) | Control (N=351) |
|---|---|---|
| Race or ethnic group — no. (%)‡ | | |
| American Indian or Alaska Native | 0 | 1 (0.3) |
| Asian | 51 (14.0) | 44 (12.5) |
| Black | 9 (2.5) | 9 (2.6) |
| Multiple | 9 (2.5) | 20 (5.7) |
| Native Hawaiian or other Pacific Islander | 1 (0.3) | 1 (0.3) |
| White | 284 (78.2) | 270 (76.9) |
| Missing | 9 (2.5) | 6 (1.7) |
| Primary tumor site — no. (%) | | |
| Hypopharynx | 28 (7.7) | 26 (7.4) |
| Larynx | 81 (22.3) | 73 (20.8) |
| Oral cavity | 219 (60.3) | 213 (60.7) |
| Oropharynx | 35 (9.6) | 38 (10.8) |
| Missing | 0 | 1 (0.3) |
| HPV status — no. (%)§ | | |
| Positive | 12 (3.3) | 15 (4.3) |
| Negative | 351 (96.7) | 335 (95.4) |
| Missing | 0 | 1 (0.3) |
| PD-L1 status — no. (%)¶ | | |
| TPS ≥50% | 103 (28.4) | 107 (30.5) |
| CPS ≥10 | 234 (64.5) | 231 (65.8) |
| CPS ≥1 | 347 (95.6) | 335 (95.4) |
| CPS <1 | 13 (3.6) | 14 (4.0) |
| Missing CPS | 3 (0.8) | 2 (0.6) |
| Current or former smoker — no. (%) | | |
| Yes | 293 (80.7) | 267 (76.1) |
| No | 64 (17.6) | 81 (23.1) |
| Missing | 6 (1.7) | 3 (0.9) |
| Alcohol use — no. (%) | | |
| Yes | 250 (68.9) | 238 (67.8) |
| No | 107 (29.5) | 110 (31.3) |
| Missing | 6 (1.7) | 3 (0.9) |

* Participants in the pembrolizumab group were assigned to receive neoadjuvant and adjuvant pembrolizumab in addition to standard care; adjuvant pembrolizumab was planned to start concomitantly with postoperative radiotherapy or chemoradiotherapy. Participants in the control group were assigned to receive standard care. Percentages may not total 100 because of rounding.

† Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with 0 indicating no symptoms and higher scores indicating greater disability.

‡ Race or ethnic group was reported by the participant.

§ Human papillomavirus (HPV) status was determined by local testing for participants with oropharyngeal cancer according to p16 immunohistochemical analysis.

¶ Programmed death ligand 1 (PD-L1) status was determined on the basis of the tumor proportion score (TPS, defined as the percentage of tumor cells with membranous PD-L1 staining) or combined positive score (CPS, defined as the number of PD-L1–staining cells, including tumor cells, lymphocytes, and macrophages, divided by the total number of viable tumor cells, multiplied by 100).

The total population was generally representative of the global population with locally advanced HNSCC (Table S4).

### EFFICACY

In the CPS-10 population, a primary end-point event occurred in 85 participants (36.3%; 25 with local progression or recurrence, 2 with local and distant progression or recurrence, 15 with distant progression or recurrence, and 43 with death) in the pembrolizumab group and in 107 participants (46.3%; 29 with local progression or recurrence, 2 with local and distant progression or recurrence, 39 with distant progression or recurrence, and 37 with death) in the control group (Fig. 1A). The median event-free survival was 59.7 months (95% confidence interval [CI], 41.1 to not reached) in the pembrolizumab group and 26.9 months (95% CI, 18.3 to 51.5) in the control group (hazard ratio for progression, recurrence, or death, 0.66; 95% CI, 0.49 to 0.88; two-sided P=0.004); the estimated percentage of participants who were alive and event-free at 3 years (36 months) was 59.8% (95% CI, 52.3 to 66.5) and 45.9% (95% CI, 38.0 to 53.4), respectively. Because the null hypothesis was rejected for event-free survival in the CPS-10 population, the next hypothesis was tested.

In the CPS-1 population, a primary end-point event occurred in 128 participants (36.9%; 37 with local progression or recurrence, 4 with local and distant progression or recurrence, 24 with distant progression or recurrence, and 63 with death) in the pembrolizumab group and 156 (46.6%; 37 with local progression or recurrence, 6 with local and distant progression or recurrence, 51 with distant progression or recurrence, and 62 with death) in the control group (Fig. 1B). The median event-free survival was 59.7 months (95% CI, 37.9 to not reached) in the pembrolizumab group and 29.6 months (95% CI, 19.5 to 41.9) in the control group (hazard ratio for progression, recurrence, or death, 0.70; 95% CI, 0.55 to 0.89; two-sided P=0.003); the estimated percentage of participants who were alive and event-free at 3 years was 58.2% (95% CI, 51.9 to 64.0) and 44.9% (95% CI, 38.4 to 51.2), respectively.

In the total population, a primary end-point event occurred in 136 participants (37.5%; 39 with local progression or recurrence, 4 local and distant progression or recurrence, 26 with distant progression or recurrence, and 67 with death) in the pembrolizumab group and 159 participants (45.3%; 37 with local progression or recurrence, 7 with local and distant progression or recurrence, 51 with distant progression or recurrence, and 64 with death) in the control group (Fig. 1C). The median event-free survival was 51.8 months (95% CI, 37.5 to not reached) in the pembrolizumab group and 30.4 months (95% CI, 21.8 to 50.1) in the control group (hazard ratio for progression, disease, or death, 0.73; 95% CI, 0.58 to 0.92; two-sided P=0.008); the estimated percentage of participants who were alive and event-free at 3 years was 57.6% (95% CI, 51.5 to 63.3) and 46.4% (95% CI, 40.0 to 52.5), respectively. The results for event-free survival according to subgroup are shown in Figure S2.

In the pembrolizumab group, a major pathological response as assessed by blinded independent pathological review occurred in 32 participants in the CPS-10 population (estimated difference in percentage of participants vs. control group, 13.7 percentage points; 95% CI, 9.7 to 18.7; P<0.001), 34 participants in the CPS-1 population (estimated difference, 9.8 percentage points; 95% CI, 7.0 to 13.3; P<0.001), and 34 participants in the total population (estimated difference, 9.3 percentage points; 95% CI, 6.7 to 12.8; P<0.001) (Table 2). In the pembrolizumab group, a pathological complete response as assessed by blinded independent pathological review occurred in 10 participants in the CPS-10 population (estimated difference in percentage of participants vs. control group, 4.2 percentage points; 95% CI, 2.1 to 7.6), 11 participants in the CPS-1 population (estimated difference, 3.1 percentage points; 95% CI, 1.6 to 5.6), and 11 participants in the total population (estimated difference, 3.0 percentage points; 95% CI, 1.5 to 5.3) (Table 2). No participants with a CPS of less than 1 or missing CPS had a major pathological response or pathological complete response.

At the first prespecified interim analysis, death had occurred in 73 participants (31.2%) in the pembrolizumab group and 89 participants (38.5%) in the control group among the CPS-10 population; 106 (30.5%) and 128 (38.2%), respectively, among the CPS-1 population; and 113 (31.1%) and 131 (37.3%), respectively, among the total population. In the CPS-10 population, the estimated overall survival at 3 years was 68.2% (95% CI, 61.3 to 74.2) in the pembrolizumab group

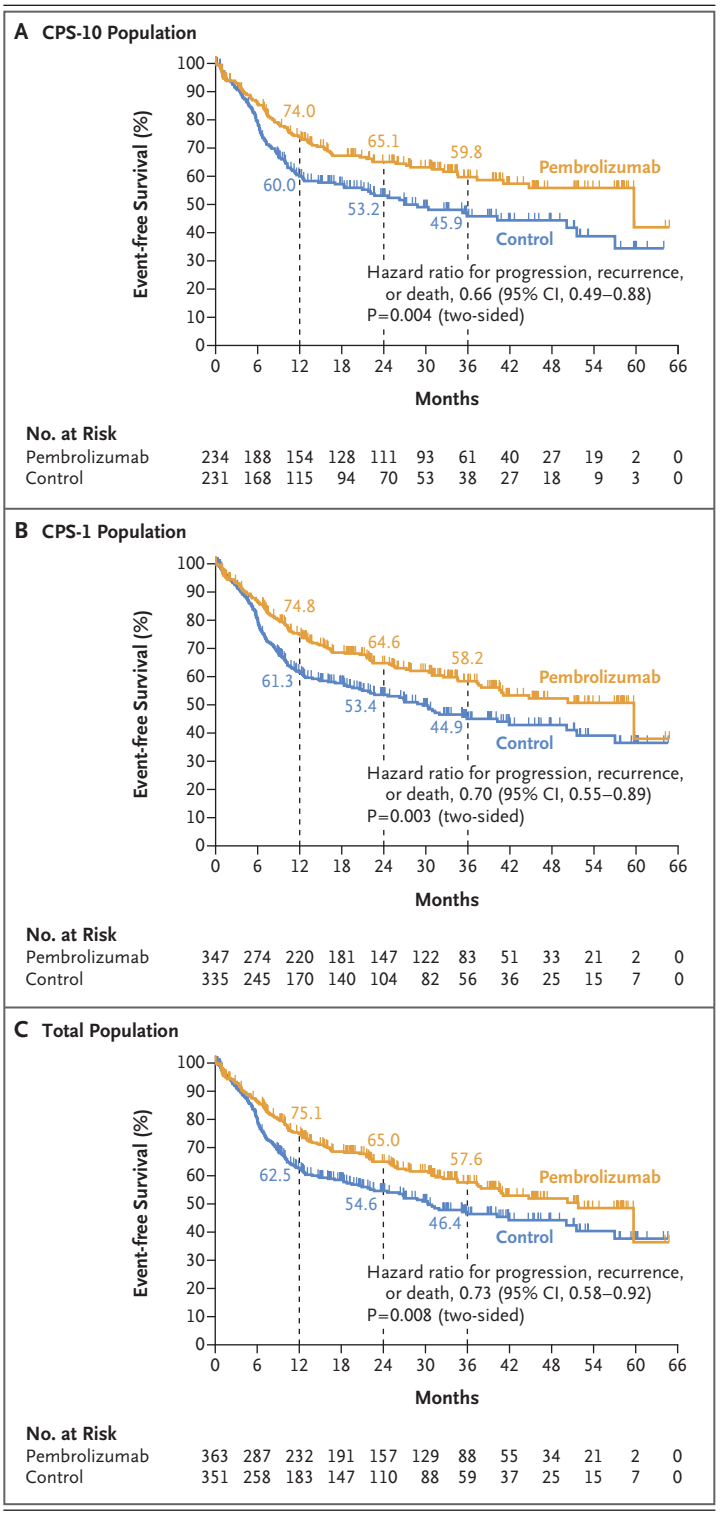



**Figure 1. Event-free Survival as Assessed by Central Review.**

Event-free survival was defined as the time from randomization to the first occurrence of disease progression or recurrence according to Response Evaluation Criteria in Solid Tumors, version 1.1, or death from any cause. Panel A shows Kaplan–Meier estimates of event-free survival among all randomly assigned participants who had tumors with a programmed death ligand 1 (PD-L1) combined positive score (CPS) of 10 or more. The CPS was defined as the number of PD-L1–staining cells, including tumor cells, lymphocytes, and macrophages, divided by the total number of viable tumor cells, multiplied by 100. Panel B shows Kaplan–Meier estimates of event-free survival among all randomly assigned participants who had tumors with a PD-L1 CPS of 1 or more. Panel C shows Kaplan–Meier estimates of event-free survival among all randomly assigned participants. Participants in the pembrolizumab group were assigned to receive neoadjuvant and adjuvant pembrolizumab in addition to standard care; adjuvant pembrolizumab was planned to start concomitantly with postoperative radiotherapy or chemoradiotherapy. Participants in the control group were assigned to receive standard care. Tick marks indicate censored data.

and 59.2% (95% CI, 51.7 to 65.9) in the control group (hazard ratio for death, 0.72; 95% CI, 0.52 to 0.98; two-sided P=0.04) (Fig. 2A). Because the protocol-specified criterion for statistical significance was not met, subsequent overall survival hypotheses were not formally tested at this time. In the CPS-1 population, the estimated overall survival at 3 years was 69.0% (95% CI, 63.3 to 74.0) in the pembrolizumab group and 60.2% (95% CI, 54.1 to 65.8) in the control group, (hazard ratio for death, 0.72; 95% CI, 0.56 to 0.94) (Fig. 2B). In the total population, the estimated overall survival at 3 years was 68.4% (95% CI, 62.9 to 73.3) and 61.1% (95% CI, 55.1 to 66.5), respectively (hazard ratio for death, 0.76; 95% CI, 0.59 to 0.98) (Fig. 2C).

### SAFETY

The as-treated population included 361 participants in the pembrolizumab group and 315 in the control group. The median total duration of therapy was 9.1 months (range, 0.03 to 22.3) and 2.9 months (range, 0.03 to 7.2), respectively (Table S5A). The median duration of adjuvant pembrolizumab was 9.7 months (range, 0.03 to 18.9), with a median of 15.0 cycles (range, 1.0 to 16.0) (Table S5C). In accordance with the trial design, adverse events were recorded from randomization to 30 days after treatment discontinuation and serious adverse events were recorded from randomization to 90 days after treatment discontinuation, which substantially

**Table 2. Pathological Response According to Blinded Independent Pathological Review.***

| End Point | CPS-10 Population (N=465) | | CPS-1 Population (N=682) | | Total Population (N=714) | |
|---|---|---|---|---|---|---|
| | Pembrolizumab (N=234) | Control (N=231) | Pembrolizumab (N=347) | Control (N=335) | Pembrolizumab (N=363) | Control (N=351) |
| Key secondary end point: major pathological response† | | | | | | |
| No. with response | 32 | 0 | 34 | 0 | 34 | 0 |
| Incidence — % (95% CI) | 13.7 (9.5–18.8) | 0.0 (0.0–1.6) | 9.8 (6.9–13.4) | 0.0 (0.0–1.1) | 9.4 (6.6–12.8) | 0.0 (0.0–1.0) |
| Estimated difference (95% CI) — percentage points‡ | 13.7 (9.7–18.7) | | 9.8 (7.0–13.3) | | 9.3 (6.7–12.8) | |
| P value | <0.001 | | <0.001 | | <0.001 | |
| Additional secondary end point: pathological complete response§ | | | | | | |
| No. with response | 10 | 0 | 11 | 0 | 11 | 0 |
| Incidence — % (95% CI) | 4.3 (2.1–7.7) | 0.0 (0.0–1.6) | 3.2 (1.6–5.6) | 0.0 (0.0–1.1) | 3.0 (1.5–5.4) | 0.0 (0.0–1.0) |
| Estimated difference (95% CI) — percentage points | 4.2 (2.1–7.6) | | 3.1 (1.6–5.6) | | 3.0 (1.5–5.3) | |

* Participants in the pembrolizumab group were assigned to receive neoadjuvant and adjuvant pembrolizumab in addition to standard care; adjuvant pembrolizumab was planned to start concomitantly with postoperative radiotherapy or chemoradiotherapy. Participants in the control group were assigned to receive standard care.

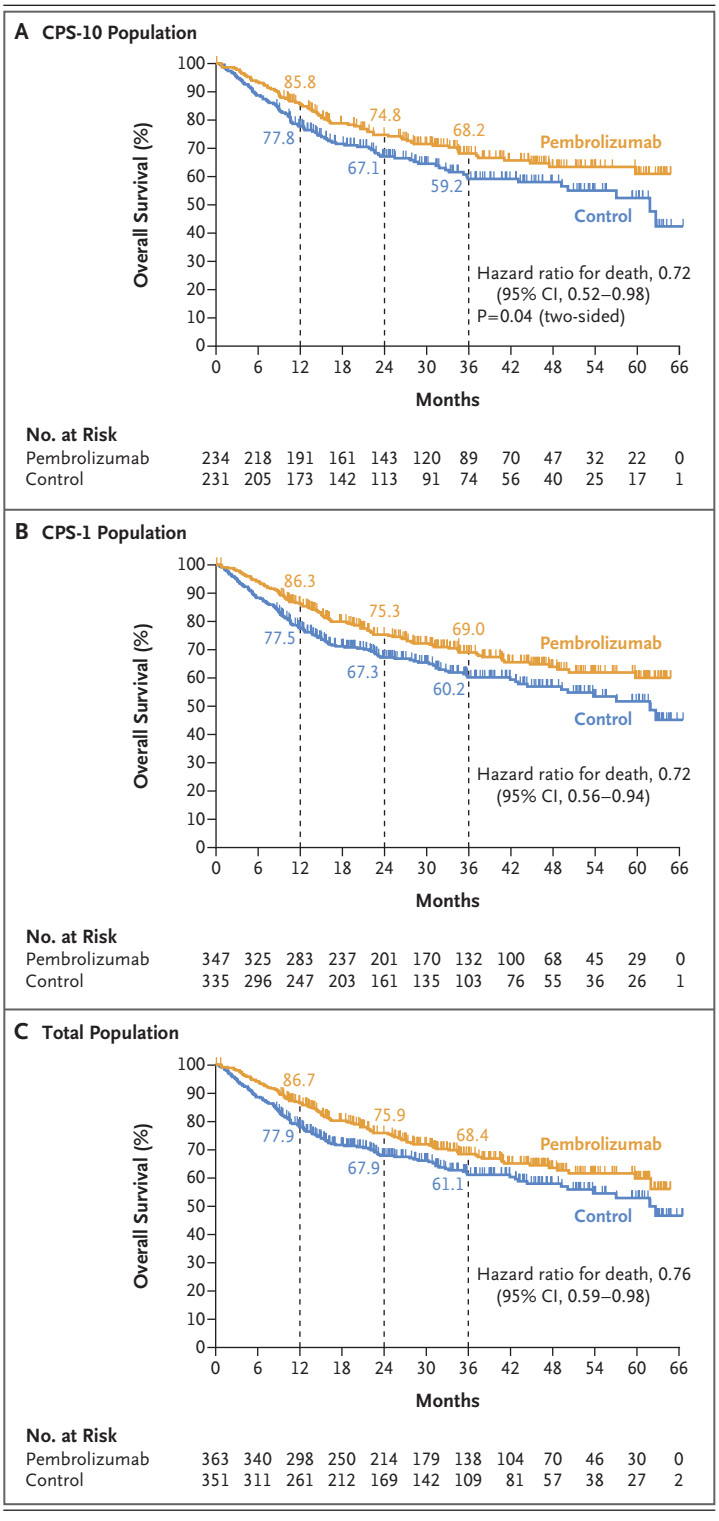
† A major pathological response was defined as having no more than 10% residual viable invasive squamous-cell carcinoma within the resected primary tumor specimen and all sampled regional lymph nodes.

‡ The estimated difference and 95% confidence interval were calculated by means of the Miettinen and Nurminen method, with stratification according to primary tumor site (oropharynx or oral cavity vs. larynx vs. hypopharynx) and tumor stage (III vs. IVA).

§ A pathological complete response was defined as having no residual invasive squamous-cell carcinoma within the resected primary tumor specimen and all sampled regional lymph nodes. Incidence was estimated by means of the Clopper–Pearson method; the between-group difference was estimated by means of the Miettinen and Nurminen stratified method.

**Figure 2. Overall Survival.**

Overall survival was defined as the time from randomization to death from any cause. Panel A shows Kaplan–Meier estimates of overall survival among all randomly assigned participants who had tumors with a PD-L1 CPS of 10 or more. Panel B shows Kaplan–Meier estimates of overall survival among all randomly assigned participants who had tumors with a PD-L1 CPS of 1 or more. Panel C shows Kaplan–Meier estimates of overall survival among all randomly assigned participants. Participants in the pembrolizumab group were assigned to receive neoadjuvant and adjuvant pembrolizumab in addition to standard care; adjuvant pembrolizumab was planned to start concomitantly with postoperative radiotherapy or chemoradiotherapy. Participants in the control group were assigned to receive standard care. Tick marks indicate censored data.




extended the monitoring window for the pembrolizumab group.

Treatment-related adverse events of any grade occurred in 81.4% of the participants in the pembrolizumab group and 81.9% of those in the control group; events of grade 3 or higher occurred in 44.6% and 42.9%, respectively (Table 3). In both groups, the most common treatment-related adverse event of grade 3 or higher was stomatitis (11.6% in the pembrolizumab group and 13.3% in the control group) (Table S6). Treatment-related serious adverse events occurred in 19.1% of the participants in the pembrolizumab group and 10.5% of those in the control group (Table 3 and Table S7); serious adverse events of any cause occurred in 49.6% and 36.8%, respectively (Table S8). Deaths attributed to treatment-related adverse events occurred in four participants (1.1%) in the pembrolizumab group (one each from renal failure, coronavirus disease 2019–related pneumonia, pneumonitis, and unknown cause) and one participant (0.3%) in the control group (acute kidney injury).

Treatment-related adverse events led to treatment discontinuation in 17.7% of the participants in the pembrolizumab group and 12.4% of those in the control group (Table 3 and Table S9). The most common event leading to discontinuation of radiotherapy was stomatitis in the pembrolizumab group (0.7%) and an increased alanine aminotransferase level in the control group (0.4%); the most common event leading to discontinuation of cisplatin was decreased neutrophil count in both groups (5.6% and 7.2%, respectively); and the most common event leading to discontinuation of pembrolizumab was pneumonitis (1.9%). Treatment-related adverse events that occurred in at least 1% of the participants in

**Table 3. Summary of Treatment-Related Adverse Events in the As-Treated Population.***

| Event | Pembrolizumab (N=361) | | Control (N=315) | |
|---|---|---|---|---|
| | Any Grade | Grade ≥3 | Any Grade | Grade ≥3 |
| | *number of participants (percent)* | | | |
| Any adverse event | 294 (81.4) | 161 (44.6) | 258 (81.9) | 135 (42.9) |
| Discontinuation of trial treatment due to adverse event | 64 (17.7) | | 39 (12.4) | |
| Death due to adverse event | 4 (1.1) | | 1 (0.3) | |
| Serious adverse event | 69 (19.1) | | 33 (10.5) | |
| Adverse events occurring in ≥5% of participants in either group | | | | |
| Radiation skin injury | 142 (39.3) | 15 (4.2) | 148 (47.0) | 18 (5.7) |
| Stomatitis | 140 (38.8) | 42 (11.6) | 164 (52.1) | 42 (13.3) |
| Hypothyroidism | 70 (19.4) | 0 | 6 (1.9) | 0 |
| Fatigue | 65 (18.0) | 3 (0.8) | 41 (13.0) | 2 (0.6) |
| Nausea | 64 (17.7) | 5 (1.4) | 67 (21.3) | 8 (2.5) |
| Dry mouth | 63 (17.5) | 3 (0.8) | 68 (21.6) | 3 (1.0) |
| Dysgeusia | 46 (12.7) | 0 | 56 (17.8) | 2 (0.6) |
| Neutrophil count decreased | 42 (11.6) | 19 (5.3) | 59 (18.7) | 37 (11.7) |
| Lymphocyte count decreased | 41 (11.4) | 20 (5.5) | 28 (8.9) | 21 (6.7) |
| Vomiting | 39 (10.8) | 1 (0.3) | 25 (7.9) | 2 (0.6) |
| White-cell count decreased | 39 (10.8) | 13 (3.6) | 50 (15.9) | 28 (8.9) |
| Dysphagia | 37 (10.2) | 10 (2.8) | 49 (15.6) | 10 (3.2) |
| Weight decreased | 35 (9.7) | 11 (3.0) | 34 (10.8) | 12 (3.8) |
| Anemia | 32 (8.9) | 8 (2.2) | 34 (10.8) | 3 (1.0) |
| Decreased appetite | 30 (8.3) | 4 (1.1) | 29 (9.2) | 4 (1.3) |
| Pruritus | 29 (8.0) | 2 (0.6) | 1 (0.3) | 0 |
| Rash | 29 (8.0) | 1 (0.3) | 0 | 0 |
| Hyperthyroidism | 27 (7.5) | 0 | 5 (1.6) | 0 |
| Alanine aminotransferase level increased | 23 (6.4) | 5 (1.4) | 16 (5.1) | 4 (1.3) |
| Diarrhea | 23 (6.4) | 3 (0.8) | 7 (2.2) | 0 |
| Oral candidiasis | 23 (6.4) | 0 | 15 (4.8) | 0 |
| Dermatitis | 21 (5.8) | 1 (0.3) | 15 (4.8) | 5 (1.6) |
| Odynophagia | 21 (5.8) | 2 (0.6) | 25 (7.9) | 0 |
| Aspartate aminotransferase level increased | 20 (5.5) | 1 (0.3) | 8 (2.5) | 1 (0.3) |
| Asthenia | 19 (5.3) | 1 (0.3) | 19 (6.0) | 2 (0.6) |
| Oral pain | 19 (5.3) | 0 | 17 (5.4) | 1 (0.3) |
| Pneumonitis | 19 (5.3) | 5 (1.4) | 0 | 0 |
| Blood creatinine level increased | 16 (4.4) | 2 (0.6) | 16 (5.1) | 2 (0.6) |
| Pharyngeal inflammation | 15 (4.2) | 0 | 19 (6.0) | 0 |
| Platelet count decreased | 14 (3.9) | 3 (0.8) | 24 (7.6) | 2 (0.6) |

* The as-treated population was defined as all the participants who received at least one dose of trial treatment or underwent surgery. The relatedness of adverse events to the trial treatment was determined by the investigators. Participants in the pembrolizumab group were assigned to receive neoadjuvant and adjuvant pembrolizumab in addition to standard care; adjuvant pembrolizumab was planned to start concomitantly with postoperative radiotherapy or chemoradiotherapy. Participants in the control group were assigned to receive standard care.

either group during the adjuvant treatment phase are shown in Table S10.

Potentially immune-mediated adverse events of any grade occurred in 43.2% of the participants in the pembrolizumab group and 10.2% of those in the control group (Table S11). In both groups, the most common such event was hypothyroidism (24.7% in the pembrolizumab group and 5.4% in the control group). Potentially immune-mediated adverse events of grade 3 or higher occurred in 10.0% of the participants in the pembrolizumab group (including six participants with pneumonitis, one of whom had a grade 5 event) and 0.6% of those in the control group.

## DISCUSSION

The phase 3, randomized KEYNOTE-689 trial showed that neoadjuvant, concomitant with postoperative radiotherapy or chemoradiotherapy, and adjuvant pembrolizumab added to standard care resulted in a significant improvement in event-free survival among participants with locally advanced HNSCC with a CPS of 10 or more, a CPS of 1 or more, and any CPS status, although the small group of participants with missing CPS data or a CPS of less than 1 limits definitive statements about the treatment effect in this population at this time. The Kaplan–Meier curves for event-free survival for all three populations separated early and remained separated, with a difference of 10 percentage points or more beyond 12 months for the duration of available trial follow-up. A major pathological response or pathological complete response was observed in 9.4% and 3.0% of the participants, respectively, in the total population of the pembrolizumab group after neoadjuvant therapy and surgery. As expected, no major pathological response or pathological complete response as assessed by blinded independent pathological review was observed in the control group. The small group of participants with a CPS of less than 1 also showed no major pathological response or pathological complete response. Results for overall survival were not mature at the first prespecified interim analysis; additional follow-up is ongoing, and testing of overall-survival hypotheses is planned for future analyses according to the statistical analysis plan.

Most treatment-related adverse events, including those of grade 3 or higher, were similar in the two groups and are known to be associated with radiotherapy or chemoradiotherapy (e.g., stomatitis, radiation skin injury, and decreased neutrophil count). Participants in the pembrolizumab group, as compared with those in the control group, had more potentially immune-mediated adverse events of any grade (43.2% vs. 10.2%) and grade 3 or higher (10.0% vs. 0.6%) and treatment-related serious adverse events (19.1% vs. 10.5%), findings consistent with reports from similar trials.[10,11,17] Of note, the duration of therapy in the pembrolizumab group was approximately triple that in the control group, which reflects the trial design and extends the therapeutic and adverse-event reporting windows. Nevertheless, the risk of serious immune-mediated toxic effects with immunotherapy is acknowledged and should be incorporated into discussions between patients and their treating physicians during treatment planning.

Historically, the addition of immune checkpoint inhibitors to standard-care radiotherapy or chemoradiotherapy in patients with nonoperated locally advanced HNSCC has not resulted in significant efficacy improvement, on the basis of the KEYNOTE-412 trial (pembrolizumab–chemoradiotherapy vs. chemoradiotherapy),[18] the JAVELIN Head and Neck 100 trial (avelumab–chemoradiotherapy vs. chemoradiotherapy),[19] the GORTEC 2015-01 PembroRad trial (pembrolizumab–radiotherapy vs. cetuximab–radiotherapy),[20] and the GORTEC 2017-01 REACH cisplatin-eligible and cisplatin-ineligible cohorts (avelumab–cetuximab–radiotherapy vs. cisplatin–radiotherapy or cetuximab–radiotherapy, respectively).[21] Atezolizumab maintenance after definitive treatment that could include surgery and radiotherapy or chemoradiotherapy also did not show a benefit with respect to event-free survival.[22] The results of the KEYNOTE-689 trial, and the recently announced significant improvement in disease-free survival in the GORTEC 2018-01 NIVOPOSTOP trial (postoperative nivolumab–chemoradiotherapy vs. chemoradiotherapy),[23] are encouraging and suggest a specific function of immune checkpoint inhibitors in targeting micrometastatic or minimally residual head and neck cancer after curative surgical therapy. Of note, the KEYNOTE-689 trial included participants with high- and low-risk disease on the basis of risk assessment guided by pathological findings, whereas the NIVOPOSTOP trial included

only those with high-risk disease. The role of the neoadjuvant component of the KEYNOTE-689 regimen in pathological tumor response and potential immunogenic priming of the tumor microenvironment are of high interest and warrant further investigation beyond the scope of this trial.

A limitation of this analysis is the difficulty in determining the specific efficacy and safety contributions of neoadjuvant pembrolizumab, concomitant with radiotherapy or chemoradiotherapy, and adjuvant pembrolizumab after radiotherapy. Similar percentages of participants in each group completed in-trial surgery (88.4% in the pembrolizumab group and 87.7% in the control group) and initiated postoperative therapy (73.6% and 76.1%, respectively), which suggests that two cycles of neoadjuvant pembrolizumab did not interfere with the ability to receive standard care. In addition, the percentage of participants who had high-risk pathological features was lower by 11.9 percentage points in the pembrolizumab group than in the control group, and the percentage who received cisplatin after surgery was lower by 11.6 percentage points; these findings indicate the possible contribution of neoadjuvant pembrolizumab. It should be noted that the monitoring window for progressive disease from randomization to the start of adjuvant therapy was longer in the pembrolizumab group than in the control group (attributable to the trial design), which potentially led to imbalances in the reasons for discontinuation before the adjuvant phase.

A further limitation is the small size of some subgroups, including participants with HPV-positive tumors and participants whose tumors had a CPS of less than 1 or a missing CPS (both subgroups accounted for <5% of the total trial population). Real-world evidence describing the prevalence of PD-L1 expression in locally advanced HNSCC is limited; however, this trial aligns with prospective studies suggesting PD-L1 positivity of approximately 90% may be frequently encountered in previously untreated locally advanced HNSCC.[18,20] In addition, an occurrence of PD-L1 positivity above 80 to 90% was observed in retrospective studies of populations with oral-cavity cancer predominance.[24,25] Some evidence suggests that pembrolizumab may have antitumor activity in HNSCC with a CPS of less than 1.[26-28] Nevertheless, the KEYNOTE-689 trial was not powered to determine the magnitude of benefit of perioperative pembrolizumab in this subgroup, and the usefulness of this regimen remains unclear for these patients.

Standard care for resectable locally advanced HNSCC has remained relatively constant since 2004, when two pivotal randomized trials first established the addition of cisplatin to postoperative radiotherapy as the recommended treatment regimen for high-risk disease.[3,4,6] The KEYNOTE-689 trial showed that the addition of neoadjuvant and adjuvant pembrolizumab to standard care conferred a significant improvement in event-free survival among patients with resectable locally advanced HNSCC.

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## AUTHOR INFORMATION

Ravindra Uppaluri, M.D., Ph.D.,[1,2] Robert I. Haddad, M.D.,[1,2] Yungan Tao, M.D., Ph.D.,[3] Christophe Le Tourneau, M.D., Ph.D.,[4] Nancy Y. Lee, M.D.,[5] William Westra, M.D.,[6] Rebecca Chernock, M.D.,[7] Makoto Tahara, M.D., Ph.D.,[8] Kevin J. Harrington, M.B., B.S., Ph.D.,[9] Arkadiy L. Klochikhin, M.D.,[10] Irene Braña, M.D., Ph.D.,[11] Gustavo Vasconcelos Alves, M.D.,[12] Brett G. M. Hughes, M.D.,[13] Marc Oliva, M.D., Ph.D.,[14] Iane Pinto Figueiredo Lima, M.D.,[15] Tsutomu Ueda, M.D., Ph.D.,[16] Tomasz Rutkowski, M.D., Ph.D.,[17] Ursula Schroeder, M.D.,[18] Paul-Stefan Mauz, M.D.,[19] Thorsten Fuereder, M.D.,[20] Simon Laban, M.D.,[21] Nobuhiko Oridate, M.D., Ph.D.,[22] Aron Popovtzer, M.D.,[23] Nicolas Mach, M.D.,[24] Yevhen Korobko, M.D., Ph.D.,[25] Diogo Alpuim Costa, M.D.,[26] Anupama Hooda-Nehra, M.D.,[27,28] Cristina P. Rodriguez, M.D.,[29] R. Bryan Bell, M.D.,[30] Cole Manschot, Ph.D.,[31] Kimberly Benjamin, M.D.,[31] Burak Gumuscu, M.D., Ph.D.,[31] and Douglas Adkins, M.D.[32]

[1] Brigham and Women's Hospital, Harvard Medical School, Boston; [2] Dana–Farber Cancer Institute, Boston; [3] Institut Gustave Roussy, Villejuif, France; [4] Institut Curie, Paris; [5] Memorial Sloan Kettering Cancer Center, New York; [6] Icahn School of Medicine at Mount Sinai Hospital, New York; [7] Washington University School of Medicine, St. Louis; [8] National Cancer Center Hospital East, Kashiwa, Japan; [9] Institute of Cancer Research, Royal Marsden Hospital, London; [10] State Budgetary Institution of Healthcare, Yaroslavl Oncological Hospital, Yaroslavl, Russia; [11] Vall d'Hebron Institute of Oncology, Vall d'Hebron University Hospital, Barcelona; [12] Centro Integrado

de Pesquisa em Oncologia, Hospital Nossa Senhora de Conceição, Porto Alegre, Brazil; [13] Royal Brisbane and Women's Hospital, University of Queensland, Brisbane, Australia; [14] Institut Català d'Oncologia L'Hospitalet, Institut d'Investigació Biomèdica de Bellvitge, Barcelona; [15] Centro Regional Integrado de Oncologia, Fortaleza, Brazil; [16] Hiroshima University Hospital, Hiroshima, Japan; [17] Maria Sklodowska-Curie National Research Institute of Oncology Gliwice Branch, Gliwice, Poland; [18] Department of Otorhinolaryngology, University of Lübeck, Lübeck, Germany; [19] Department of Otolaryngology, Head and Neck Surgery, University Hospital Tübingen, Tübingen, Germany; [20] Department of Medicine I, Division of Oncology, Medical University of Vienna, Vienna; [21] Department of Otorhinolaryngology and Head and Neck Surgery, Ulm University Medical Center and Comprehensive Cancer Center Ulm, Ulm, Germany; [22] Yokohama City University School of Medicine, Yokohama, Japan; [23] Hadassah Medical Center, Jerusalem; [24] Geneva University Hospital, University of Geneva, Geneva; [25] National Cancer Institute, Kyiv, Ukraine; [26] Hospital CUF Descobertas, Lisbon, Portugal; [27] Rutgers Cancer Institute, Newark, NJ; [28] Division of Hematology–Oncology, Department of Medicine, Rutgers New Jersey Medical School, Newark; [29] Fred Hutchinson Cancer Center, University of Washington, Seattle; [30] Providence Cancer Institute, Earle A. Chiles Research Institute, Portland, OR; [31] Merck, Rahway, NJ; [32] Robert Ebert and Greg Stubblefield Head and Neck Tumor Center at Washington University School of Medicine, Alvin J. Siteman Cancer Center, and Barnes–Jewish Hospital, St. Louis.

## REFERENCES

**1.** National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: head and neck cancers. Version 3.2025. (https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1437).

**2.** Machiels J-P, René Leemans C, Golusinski W, et al. Squamous cell carcinoma of the oral cavity, larynx, oropharynx and hypopharynx: EHNS-ESMO-ESTRO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2020;31:1462-75.

**3.** Bernier J, Domenge 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.** Adelstein DJ, Li Y, Adams GL, et al. An intergroup phase III comparison of standard radiation therapy and two schedules of concurrent chemoradiotherapy in patients with unresectable squamous cell head and neck cancer. J Clin Oncol 2003;21:92-8.

**6.** Bernier J, Cooper JS, Pajak TF, et al. Defining risk levels in locally advanced head and neck cancers: a comparative analysis of concurrent postoperative radiation plus chemotherapy trials of the EORTC (#22931) and RTOG (# 9501). Head Neck 2005;27:843-50.

**7.** Burtness B, Harrington KJ, Greil R, et al. Pembrolizumab alone or with chemotherapy versus cetuximab with chemotherapy for recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-048): a randomised, open-label, phase 3 study. Lancet 2019;394:1915-28.

**8.** Choueiri TK, Tomczak P, Park SH, et al. Overall survival with adjuvant pembrolizumab in renal-cell carcinoma. N Engl J Med 2024;390:1359-71.

**9.** Schmid P, Cortes J, Dent R, et al. Overall survival with pembrolizumab in early-stage triple-negative breast cancer. N Engl J Med 2024;391:1981-91.

**10.** Lorusso D, Xiang Y, Hasegawa K, et al. Pembrolizumab or placebo with chemoradiotherapy followed by pembrolizumab or placebo for newly diagnosed, high-risk, locally advanced cervical cancer (ENGOT-cx11/GOG-3047/KEYNOTE-A18): overall survival results from a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 2024;404:1321-32.

**11.** Wakelee H, Liberman M, Kato T, et al. Perioperative pembrolizumab for early-stage non–small-cell lung cancer. N Engl J Med 2023;389:491-503.

**12.** Eggermont AMM, Blank CU, Mandala M, et al. Adjuvant pembrolizumab versus placebo in resected stage III melanoma. N Engl J Med 2018;378:1789-801.

**13.** Uppaluri R, Campbell KM, Egloff AM, et al. Neoadjuvant and adjuvant pembrolizumab in resectable locally advanced, human papillomavirus–unrelated head and neck cancer: a multicenter, phase II trial. Clin Cancer Res 2020;26:5140-52.

**14.** Wise-Draper TM, Gulati S, Palackdharry S, et al. Phase II clinical trial of neoadjuvant and adjuvant pembrolizumab in resectable local-regionally advanced head and neck squamous cell carcinoma. Clin Cancer Res 2022;28:1345-52.

**15.** Oliveira G, Egloff AM, Afeyan AB, et al. Preexisting tumor-resident T cells with cytotoxic potential associate with response to neoadjuvant anti-PD-1 in head and neck cancer. Sci Immunol 2023;8(87):eadf4968.

**16.** Maurer W, Bretz F. Multiple testing in group sequential trials using graphical approaches. Stat Biopharm Res 2013;5:311-20 (https://www.tandfonline.com/doi/abs/10.1080/19466315.2013.807748).

**17.** Schmid P, Cortes J, Pusztai L, et al. Pembrolizumab for early triple-negative breast cancer. N Engl J Med 2020;382:810-21.

**18.** Machiels JP, Tao Y, Licitra L, et al. Pembrolizumab plus concurrent chemoradiotherapy versus placebo plus concurrent chemoradiotherapy in patients with locally advanced squamous cell carcinoma of the head and neck (KEYNOTE-412): a randomised, double-blind, phase 3 trial. Lancet Oncol 2024;25:572-87.

**19.** Lee NY, Ferris RL, Psyrri A, et al. Avelumab plus standard-of-care chemoradiotherapy versus chemoradiotherapy alone in patients with locally advanced squamous cell carcinoma of the head and neck: a randomised, double-blind, placebo-controlled, multicentre, phase 3 trial. Lancet Oncol 2021;22:450-62.

**20.** Tao Y, Biau J, Sun XS, et al. Pembrolizumab versus cetuximab concurrent with radiotherapy in patients with locally advanced squamous cell carcinoma of head and neck unfit for cisplatin (GORTEC 2015-01 PembroRad): a multicenter, randomized, phase II trial. Ann Oncol 2023;34:101-10.

**21.** Tao Y, Auperin A, Sun X, et al. Avelumab-cetuximab-radiotherapy (RT) versus standards of care in patients with locally advanced squamous cell carcinoma of head and neck (LA-SCCHN): final analysis of randomized phase III GORTEC 2017-01 REACH trial. Ann Oncol 2024;35:Suppl 2:S616 (https://www.annalsofoncology.org/article/S0923-7534(24)02434-7/fulltext).

**22.** Wong DJ, Fayette J, Teixeira M, et al. Abstract CT009: IMvoke010: a phase III, double-blind randomized trial of atezolizumab (atezo) after definitive local therapy vs placebo in patients (pts) with high-risk locally advanced (LA) squamous cell carcinoma of the head and neck (SCCHN). Cancer Res 2024;84:Suppl 7:CT009 (https://aacrjournals.org/cancerres/article/84/7_Supplement/CT009/742401/Abstract-CT009-IMvoke010-A-phase-III-double-blind).

**23.** Sava J. Post-operative nivolumab significantly improves DFS in head and neck cancer. Targeted Oncology, January 10, 2025 (https://www.targetedonc.com/view/post-operative-nivolumab-significantly-improves-dfs-in-head-and-neck-cancer).

**24.** Troeltzsch M, Woodlock T, Pianka A, et al. Is there evidence for the presence and relevance of the PD-1/PD-L1 pathway in oral squamous cell carcinoma? Hints from an immunohistochemical study. J Oral Maxillofac Surg 2017;75:969-77.
**25.** Tan H, Huang W, Long Y, et al. Analysis of PD-L1 expression in locally advanced head and neck squamous cell carcinoma and its correlation with the efficacy of neoadjuvant immunotherapy + chemotherapy: a retrospective real-world study. J Clin Oncol 2024;42:Suppl (https://ascopubs.org/doi/10.1200/JCO.2024.42.16_suppl.6074).
**26.** Bauml J, Seiwert TY, Pfister DG, et al. Pembrolizumab for platinum- and cetuximab-refractory head and neck cancer: results from a single-arm, phase II study. J Clin Oncol 2017;35:1542-9.
**27.** Chow LQM, Haddad R, Gupta S, et al. Antitumor activity of pembrolizumab in biomarker-unselected patients with recurrent and/or metastatic head and neck squamous cell carcinoma: results from the phase Ib KEYNOTE-012 expansion cohort. J Clin Oncol 2016;34:3838-45.
**28.** Burtness B, Rischin D, Greil R, et al. Pembrolizumab alone or with chemotherapy for recurrent/metastatic head and neck squamous cell carcinoma in KEYNOTE-048: subgroup analysis by programmed death ligand-1 combined positive score. J Clin Oncol 2022;40:2321-32.