# Nivolumab added to cisplatin and radiotherapy versus cisplatin and radiotherapy alone after surgery for people with squamous cell carcinoma of the head and neck at a high risk of relapse (GORTEC 2018-01 NIVOPOST-OP): a randomised, open-label, phase 3 trial

*Jean Bourhis*, Anne Aupérin*, Christian Borel, Gautier Lefebvre, Severine Racadot, Lionnel Geoffrois, Xu Shan Sun, Esma Saada, Beatriz Cirauqui, Tomasz Rutkowski, Stephanie Henry, Anouchka Modesto, Alison Johnson, Sophie Chapet, Benoit Calderon, Christian Sire, Olivier Malard, Matthieu Bainaud, Antonio Da Silva Motta, Sebastien Thureau, Yoann Pointreau, Pierre Blanchard, Guillaume Buiret, Laurence Bozec, Stephane Lopez, Julie Vanbockstael, Matthieu Bosset, Charlotte Greilsamer, Amaury Daste, Antoine Bruna, France N'Guyen, Maria Plana, Eluska Iruarrizaga, Stephane Temam, Caroline Even, Elisabeth Perez Ruiz, Mahasti Bert, Eleni Karamouza, Juliette Thariat, Joanna Kazmierska, Amanda Psyrri, Ricard Mesia†, Yungan Tao†*

## Summary

**Background** Postoperative cisplatin and radiotherapy is the standard of care for high-risk resected locally advanced squamous cell carcinoma of the head and neck (LA-SCCHN). The NIVOPOST-OP trial aimed to assess the efficacy and safety of programmed death 1 blockade by nivolumab added to cisplatin and radiotherapy in this setting.

**Methods** This open-label, phase 3 trial evaluated adding nivolumab to cisplatin and radiotherapy after surgery for LA-SCCHN with high-risk pathological features. The main inclusion criteria were age 19–74 years, an Eastern Cooperative Oncology Group performance status 0–1, squamous cell carcinoma of the oral cavity, oropharynx, larynx, or hypopharynx resected with macroscopic complete resection, and at least one high-risk pathological feature: nodal extracapsular extension, microscopically positive margins, four or more cervical nodal involvements without extracapsular extension, and multiple perineural invasions. 680 participants recruited in 82 sites across six countries (France, Spain, Poland, Belgium, Greece, and Switzerland) were randomly assigned 1:1 to receive cisplatin and radiotherapy (66 Gy, cisplatin 100 mg/m² intravenously once every 3 weeks, for three cycles); or nivolumab 240 mg intravenously, followed by cisplatin and radiotherapy with three cycles of concomitant nivolumab 360 mg once every 3 weeks, and six cycles of adjuvant nivolumab 480 mg once every 4 weeks. The primary endpoint was disease-free survival as per investigator assessment in the intention-to-treat population. 230 disease-free survival events (relapses or deaths) were required to detect a hazard ratio of 0·65 with 0·05 two-sided α error, with 90% power. The trial is registered at ClinicalTrials.gov (NCT03576417) and is active, but not recruiting.

**Findings** The 680 patients were recruited from Oct 15, 2018, to July 3, 2024. The analysis was based on 666 participants randomly assigned until the cutoff date (April 30, 2024), at which point the required number of events was reached (median follow-up 30·3 months). Disease-free survival was significantly improved with nivolumab, cisplatin, and radiotherapy versus cisplatin and radiotherapy alone, irrespective of programmed death ligand 1 expression (HR 0·76; 95% CI 0·60–0·98; stratified log-rank test p value=0·034). There was an increase in the rate of participants with treatment-related grade 4 adverse events with nivolumab, cisplatin, and radiotherapy compared with cisplatin and radiotherapy (30 [10%] of 312 *vs* 16 [5%] of 306). Treatment-related deaths occurred in two participants in each group.

**Interpretation** Nivolumab added to cisplatin and radiotherapy in high-risk resected LA-SCCHN improves disease-free survival with moderate toxic effect increase, and can be proposed as a new standard treatment.

**Funding** Groupe Oncologie Radiotherapie Tete Et Cou (GORTEC) and Bristol Myers Squibb.



*Lancet* 2026; 407: 363–74

Published Online December 22, 2025 https://doi.org/10.1016/S0140-6736(25)01850-1

See Comment page 313

*Co-first authors

†Co-last authors

**Radiation Oncology Department, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland** (Prof J Bourhis MD); **Biostatistics and Epidemiology Office, Gustave Roussy, Inserm U1018 Oncostat labeled Ligue Contre le Cancer, University Paris-Saclay, Villejuif, France** (A Aupérin MD, E Karamouza PhD); **Institut De Cancérologie Strasbourg Europe, Strasbourg, France** (C Borel MD); **Centre Oscar Lambret, Lille, France** (G Lefebvre MD); **Centre Leon Bérard, Lyon, France** (S Racadot MD); **Institut de Cancérologie de Lorraine, Vandoeuvre-Lés-Nancy, France** (L Geoffrois MD); **Hopital Nord Franche Comté, Montbelliard, France** (X S Sun MD); **Centre Antoine Lacassagne, Nice, France** (E Saada MD); **Institut Català d'Oncologia Badalona, Barcelona, Spain** (B Cirauqui MD); **Maria Skłodowska-Curie Institute of Oncology, Gliwice, Poland** (T Rutkowski MD); **Centre Hospitalier Universitaire Université Catholique de Louvain Namur, Namur Site Sainte Elisabeth, Namur, Belgium** (S Henry MD); **Claudius Regaud Institute, Toulouse, France** (A Modesto MD); **Centre**

## Introduction

For more than two decades, treatment guidelines for high-risk resected locally advanced squamous cell carcinoma of the head and neck (LA-SCCHN) have recommended postoperative radiotherapy and concomitant cisplatin-based chemotherapy.[1–3] Hence, cisplatin-based chemotherapy is standard of care for patients with high-risk pathological features after resection, such as nodal extracapsular extension or positive margins.[4,5] In addition to the well established

**François Baclesse, Caen, France** (A Johnson MD, Prof J Thariat MD); **CHRU Bretonneau, Tours France** (S Chapet MD); **Institut Sainte Catherine, Avignon, France** (B Calderon MD); **Centre Hospitalier de Bretagne Sud, Lorient, France** (C Sire MD); **Centre Hospitalier Universitaire de Nantes, Nantes, France** (O Malard MD); **Centre Hospitalier Universitaire Poitiers, Poitiers, France** (M Bainaud MD); **Institut de Cancérologie Jean Godinot, Reims, France** (A Da Silva Motta MD); **Centre Henri Becquerel, Rouen, France** (S Thureau MD); **Clinique Victor Hugo-Centre Jean Bernard, Le Mans, France** (Y Pointreau MD); **Gustave Roussy, Villejuif, France** (Prof P Blanchard MD, F N'Guyen MD, S Temam MD, C Even MD); **Department of Radiation Oncology and INSERM, U1030 Molecular Radiotherapy and Therapeutic Innovations, Gustave Roussy, Villejuif, France** (Y Tao MD); **Centre Hospitalier de Valence, Valence, France** (G Buiret MD); **Institut Curie-Hopital René Huguenin, Saint Cloud, France** (L Bozec MD); **Centre Hospitalier Annecy Genevois, Pringy, France** (S Lopez MD); **Institut de Cancérologie de l'Ouest René Gauducheau, Saint Herblain, France** (J Vanbockstael MD); **Centre Marie Curie-Hôpital Privé Drôme Ardèche, Valence, France** (M Bosset MD); **Centre Hospitalier Départemental de Vendée, La Roche sur Yon, France** (C Greilsamer MD); **Centre Hospitalier Universitaire de Bordeaux, Bordeaux, France** (A Daste MD); **Hôpital Privé Sainte Marie, Chalon sur Saone, France** (A Bruna MD); **Institut Català d'Oncologia, Barcelona, Spain** (M Plana MD); **Hospital Universitario de Cruces, Barakaldo, Spain** (E Iruarrizaga MD); **Hospital Regional Universitario de Málaga, Malaga, Spain** (E Perez Ruiz MD); **GORTEC, Radiotherapy Oncology Group for Head and Neck, Tours, France** (M Bert MSc); **Gielkopolskie Centrun Onkologii im Marii Curie-Sklodowskiej Greater Poland Cancer Center, Poznan, Poland** (Prof J Kazmierska MD); **Medical Oncology, Attikon University**

## Research in context

### Evidence before this study

To identify evidence before the NIVOPOST-OP trial (initiated 2018), we searched PubMed, and American Society of Clinical Oncology and European Society For Medical Oncology abstracts published between Jan 1, 2015, and June 1, 2025, in English, for randomised trials on immunotherapy and radiotherapy in locally advanced head and neck squamous cell carcinoma (LA-SCCHN). Search terms used were "head and neck squamous cell carcinoma," "locally advanced," "immunotherapy," "radiotherapy," "PD-1/PD-L1 inhibitors," and "randomized trial".

Head and neck cancers are the 6th most common type of cancer worldwide, consisting mostly of LA-SCCHN. A large proportion of LA-SCCHN are treated by surgery and the standard postoperative treatment for high-risk resected LA-SCCHN was established in 2004 with postoperative cisplatin-based chemoradiotherapy. The magnitude of the benefit due to the addition of concomitant chemotherapy to postoperative radiotherapy is illustrated in the meta-analysis MACH-NC based on updated individual patient data, with a 9% improvement in 3-year disease-free survival. However, despite this combination of surgery followed by postoperative cisplatin-based chemotherapy, recurrence still occurs in 40–45% of people, showing an unmet clinical need.

Programmed death 1 (PD-1) inhibitors are effective treatments in SCCHN and have been established as the standard-of-care in the recurrent or metastatic setting (eg, in the CheckMate 141 and KEYNOTE-048 studies), but randomised phase 2–3 trials have not reached their efficacy endpoint in the locally advanced setting (eg, in the GORTEC 2015–01 PembroRad, NRG-HN004, JAVELIN Head and Neck 100, GORTEC 2017–01 REACH, KEYNOTE-412, and IMvoke010 studies).

In 2018, when NIVOPOST-OP (NCT03576417) was initiated, a randomised phase 3 trial evaluating the addition of both neoadjuvant and adjuvant pembrolizumab to standard-of-care for people with resectable LA-SCCHN (KEYNOTE-689, NCT03765918) began concurrently with our study.

### Added value of this study

To our knowledge, NIVOPOST-OP is the first large-scale randomised, phase 3 trial, evaluating the addition of anti-PD-1 nivolumab (concomitant and adjuvant) to the standard-of-care postoperative radiotherapy and concomitant cisplatin-based chemotherapy in high-risk resected LA-SCCHN. The benefit of adding nivolumab to cisplatin-based chemotherapy (HR of disease-free survival events 0·76; an increase of 10·6% in the 3-year disease-free survival rate) is similar to that of concomitant chemotherapy added to postoperative radiotherapy (hazard ratio 0·78; an increase of 9% in the 3-year event-free survival rate). The benefit of adding nivolumab was obtained along with a moderate increase in toxicity, with no increase in toxic deaths, indicating a favourable risk to benefit ratio.

### Implications of all the available evidence

NIVOPOST-OP provides strong evidence that adding nivolumab to postoperative radiotherapy and concomitant cisplatin-based chemotherapy significantly improves disease-free survival in high-risk resected LA-SCCHN, addressing a 20-year therapeutic gap since radiotherapy and concomitant cisplatin-based chemotherapy became standard. Unlike previous LA-SCCHN trials with negative results, NIVOPOST-OP highlights the efficacy of PD-1 inhibition in the postoperative setting. Its favorable risk–benefit profile supports adopting nivolumab plus radiotherapy and concomitant cisplatin-based chemotherapy as a new standard of care, offering a strategy to reduce recurrence.

high-risk pathological features of nodal extracapsular extension and positive margins, additional high-risk pathological factors have been described, such as multiple perineural invasions[6] or multiple cervical node involvement.[7] Despite extensive surgery followed by high-dose cisplatin and radiotherapy, up to 40–45% of patients develop locoregional recurrence or distant metastases, or both, within 2 years of completing treatment.[1–3,8,9]

Programmed death 1 (PD-1) blockade has recently emerged as an effective therapy for people with SCCHN in the recurrent or metastatic setting,[10] hence creating a new standard of care, especially in first-line recurrent or metastatic SCCHN.[11] In parallel, these immune checkpoint inhibitors were tested in people with non-metastatic LA-SCCHN. In large-scale randomised trials, blockade of PD-1 or its ligand (PD-L1) in combination with cisplatin-based chemotherapy,[12–14] radiotherapy,[15] or cetuximab and radiotherapy[16] did not improve outcomes versus standard of care in people with unresected LA-SCCHN. All these trials were performed in all people without selection based on PD-L1 combined positive score, and post-hoc analyses in subgroups of patients defined by PD-L1 combined positive score could not clearly identify a subset of people that would benefit from this PD-1 and PD-L1 targeted therapy.[12–15]

In contrast with these trials done in people with unresected or unresectable bulky disease, we conducted a randomised phase 3 trial, Groupe Oncologie Radiotherapie Tete Et Cou (GORTEC) 2018-01 NIVOPOST-OP (hereafter referred to as the NIVOPOST-OP study), in people without macroscopic residual disease after surgery to establish whether PD-1 blockade with nivolumab added to standard-of-care postoperative radiotherapy and concomitant

cisplatin-based chemotherapy could improve disease-free survival for high-risk resected LA-SCCHN.

## Methods

### Study design and participants

NIVOPOST-OP was a multicentre, international, randomised, open-label, phase 3 trial sponsored by the French Head and Neck Oncology Radiotherapy group, GORTEC, and it enrolled patients from 82 sites (cancer centres, university hospitals, and public and private general hospitals) across six European countries (Belgium, France, Greece, Poland, Spain, and Switzerland; appendix pp 2–6). This study is registered with ClinicalTrials.gov (NCT03576417) and is active but not recruiting.

Eligible participants were older than 18 years and younger than 75 years, had an Eastern Cooperative Oncology Group performance status of 0–1, and had squamous cell carcinoma (SCC) of the oral cavity, oropharynx, larynx, or hypopharynx. Participants should have undergone macroscopic complete resection and be disease free at the time of random assignment. All participants were at a high risk of relapse after surgery, defined by a combination of an advanced pathological stage with high-risk pathological features. Participants with a pathological stage III or IV as per the American Joint Committee on Cancer, 8th edition, were eligible, as well as a pathological stage II p16-positive oropharyngeal SCC, but only if their staging code was pT3N1 or pT4N1, and if tobacco consumption was 20 or more pack-years. The presence of pathological high-risk relapse factors was necessary for inclusion, defined by any or all of the following: nodal extracapsular extension, microscopically positive margins (R1 or a close margin of ≤1 mm), four or more cervical nodal involvements without extracapsular extension, and multiple perineural invasions as stated in the local pathological report. Other eligibility criteria included adequate organ function to receive three cycles of high-dose cisplatin, peripheral neuropathy of grade 1 or less, no hearing loss (assessed clinically and confirmed by audiogram if doubtful), and cardiac function compatible with hyperhydration. Key exclusion criteria were: nasopharyngeal, paranasal sinuses, nasal cavity tumours, or thyroid cancers; SCC involving cervical neck nodes with an unknown primary site; metastatic disease; incomplete macroscopic resection (R2) as stated in the local surgical report; and any previous treatment for the current head and neck cancer other than primary surgery. All participants provided written informed consent before entering the trial. The complete list of eligibility criteria is in the appendix (pp 8–9).

Sex data were self-reported in medical records. Ethnicity data were not collected because, in France, their collection requires authorisation and should be justified to be necessary for the study aims, which was not the case in NIVOPOST-OP.

The study was performed in accordance with the International Conference on Harmonization of Good Clinical Practice Guidelines and the principles of the Declaration of Helsinki, and was approved by competent authorities and ethics committees (approval number EC Ouest VI N°1092; appendix p 7). An international, independent data monitoring committee, composed of an ear, nose, and throat surgeon, a radiation oncologist, a medical oncologist, and a statistician reviewed the safety data during the study (appendix p 7).

### Randomisation and masking

Eligible participants were randomly assigned in a 1:1 ratio using CleanWeb Interactive Response Technology by investigators or duly authorised people to receive cisplatin plus radiotherapy or cisplatin plus radiotherapy plus nivolumab, with minimisation by p16 status (p16-positive oropharyngeal cancer *vs* p16-negative oropharyngeal cancer or not oropharyngeal cancer) and site of recruitment. To avoid deterministic minimisation and ensure allocation concealment, the treatment that minimised imbalance was assigned with a probability of 0·80. Physicians and participants were not masked to treatment group.

### Procedures

In the control group, participants received the standard-of-care radiotherapy (done by intensity modulated radiotherapy) at 66 Gy in 33 fractions with concomitant cisplatin (100 mg/m² intravenously) once every 3 weeks for three cycles (cisplatin plus radiotherapy group). In the experimental group, participants received a first intravenous administration of nivolumab (240 mg) a minimum of 2 weeks after surgery, followed by standard-of-care cisplatin plus radiotherapy (starting 10–14 days after the first nivolumab administration) with three cycles of concomitant nivolumab 360 mg intravenously once every 3 weeks (±3 days) followed by six administrations of adjuvant nivolumab 480 mg intravenously once every 4 weeks (±5 days) in an overall recommended timeframe of 6 months (nivolumab plus cisplatin plus radiotherapy group; appendix p 10). Nivolumab was supplied by Bristol Myers Squibb (Princeton, NJ, USA). Participants had to start radiotherapy and concomitant cisplatin within 4–10 weeks after surgery.

Radiotherapy quality assurance was performed by two radiation oncologist experts who were masked to the treatment allocation. The main data reviewed were dose and volume conformity.

After surgery, head and neck and chest CT scans were performed before random assignment to ensure that participants were disease free. During follow-up, clinical examination, endonasal fibroscopy, and head and neck CT or MRI were performed along with a chest CT scan (and optional [$^{18}$F]fluorodeoxyglucose-PET scanner) at 3-month intervals during the first year, every 4 months in the second and third years, and every 6 months thereafter

**Hospital, Athens, Greece** (Prof A Psyrri MD); **Institut Català d'Oncologia, Institut de Recerca Germans Trias i Pujol, Badalona, Spain** (Prof R Mesia MD)

Correspondence to:
Dr Yungan Tao, Department of Radiation Oncology and INSERM, U1030 Molecular Radiotherapy and Therapeutic Innovations, Gustave Roussy, Villejuif 94800, France
**yungan.tao@gustaveroussy.fr**

or

Prof Jean Bourhis, Radiation Oncology Department, Centre Hospitalier Universitaire Vaudois, Lausanne 1011, Switzerland
**jean.bourhis@chuv.ch**

See **Online** for appendix

in the fourth and fifth years. Endoscopy under general anaesthesia and biopsies were performed if appropriate for confirmation of a local relapse. PD-L1 status was analysed centrally (Labcorp, Geneva, Switzerland) using the Dako PD-L1 immunohistochemistry 28–8 pharmDx assay (Agilent Technologies, Santa Clara, CA, USA). Protocol deviations were monitored by the sponsor.

### Outcomes

The primary endpoint was disease-free survival, defined as the time between random assignment and first event among local, regional, or distant relapse as assessed by investigators, and death, whatever the cause of death. Participants who did not have these events were censored at the date of last disease evaluation. Local or regional relapses were confirmed by pathology unless not medically indicated, or if the lesion location made it unsafe for biopsy. Confirmation of pathology was recommended in the case of solitary metastasis (especially in the lung and bone).

Secondary endpoints were overall survival, defined as the time from random assignment to the date of death from any cause; cumulative incidences of locoregional relapses, distant metastases, and deaths without previous disease relapse; disease-free survival using a masked independent central review; incidence of second primary malignancies; and safety. The events taken into account in disease-free survival by independent central review were lesions identified by the masked independent central review on imaging and deaths from any cause. Independent central review was performed by CLARIO radiologists who were masked to the treatment group and without any clinical, endoscopic, or pathological information. For distant lesions, masked independent central review did not distinguish metastases of the studied SCCHN from a new primary malignancy. Participants who did not have an event were censored at the date of last imaging available for masked independent central review. Safety assessment was based on the incidence of adverse events, serious adverse events, and adverse events leading to treatment discontinuation. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0. Monitoring of adverse events was shared with the independent data monitoring committee. The following study periods were considered for safety analyses: adverse events occurring up to 100 days after last treatment of lead-in and concomitant phases, adverse events occurring over the period from 101 days to 273 days (9 months) after last treatment of lead-in and concomitant phases, and adverse events after 9 months with long-term follow-up. Health-related quality of life as assessed by the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire core module and Head and Neck module questionnaires was an exploratory endpoint, which will be reported elsewhere.

For **CLARIO** see https://clario.com/

### Statistical analysis

Anticipating that the population of participants who would be included in the trial would be predominantly smokers with 16-negative tumours and based on large-scale randomised trials for postoperative radiotherapy in people with high-risk LA-SCCHN,[1,2,8] a 3-year disease-free survival of 60% was expected in the standard-of-care cisplatin plus radiotherapy group. The expected hazard ratio (HR) with nivolumab, cisplatin, and radiotherapy, compared with cisplatin and radiotherapy alone, was 0·65, corresponding to a difference in 3-year disease-free survival rate of 60·0% versus 71·7%, assuming exponential disease-free survival time distribution. Assuming a two-sided type I error of 0·05, 230 events (relapse or death) were needed to provide a 90% power to detect this HR. A total of 230 events were expected of 680 patients (340 per group).

If the comparison of disease-free survival was statistically significant, overall survival was planned to be hierarchically tested as a key secondary endpoint. To detect an HR of 0·68 at a two-sided type I error of 0·05, 242 deaths were needed to provide 85% power. The efficacy endpoint analyses were done according to the intention-to-treat principle, including all participants randomly assigned until the data cutoff (when required number of disease-free survival events was reached) and irrespective of PD-L1 expression.

Disease-free survival was compared between the treatment groups by stratified two-sided log-rank test, with the p16 minimisation factor as a stratification factor. The HR of disease-free survival events between treatment groups was estimated using a stratified Cox proportional hazards model, with treatment as the sole covariate. The assumption of proportional hazards was examined using a time-dependent variable defined by treatment group by log(time) interaction in addition to the treatment group variable in the Cox model. A two-sided Wald $\chi^2$ p value of less than 0·10 indicated the presence of non-proportional hazards. Disease-free survival was calculated using the Kaplan–Meier method. To assess the respective contribution of the different types of disease-free survival events, the cumulative incidence of locoregional relapse alone, distant relapse alone, combined locoregional and distant relapse, and death as the first event were estimated within the competing risk framework. Subdistribution HR (with 95% CI) was calculated from the Fine–Gray model stratified for the p16 minimisation factor. Incidence of second primary malignancies was calculated using the Kaplan–Meier method: the event was the occurrence of a second primary malignancy, whatever the location; relapses of the treated SCCHN were ignored and participants were censored at last follow-up or death. Prespecified exploratory analyses included analysing disease-free survival by investigators according to PD-L1 expression by combined positive score, age, sex, smoking status, alcohol consumption, baseline haemoglobin, type of risk factors of relapse,

pathological stage, primary tumour localisation, and p16 expression.

Disease-free survival by masked independent central review was analysed in the same way as disease-free survival by investigators. To correct the most obvious false negative and false positive cases of the masked independent central review, a post-hoc sensitivity analysis of disease-free survival by masked independent central review was done by adding relapses diagnosed by investigators but not by masked independent central review when they were confirmed by biopsy and histology, and by removing relapses diagnosed by masked independent central review but not by investigators in participants alive and clinically free of disease when they did not receive any new oncological treatment for 18 months or more after masked independent central review diagnosis.

Adverse events were described by treatment group, according to grade and type in the three safety periods studied. In the first period, the safety analysis included randomly assigned participants who received at least one dose of any study treatment (radiotherapy, cisplatin, and nivolumab), referred to as treated participants. In the second and third periods, the safety analyses included all treated participants who were alive at the beginning of the period.

### Role of the funding source

GORTEC designed and conducted the study; and collected, checked, analysed, and interpreted the data. Bristol Myers Squibb had no role in data collection, data analysis, data interpretation, writing of the report, and the decision to submit.

## Results

Between Oct 15, 2018, and July 3, 2024, 680 participants were randomly assigned: 341 in the cisplatin and radiotherapy group and 339 in the nivolumab, cisplatin, and radiotherapy group. Disease-free survival analysis was done when the required number of disease-free survival events was reached. The data cutoff date was on April 30, 2024, and the analysis was considered as final for the primary endpoint and based on 666 participants randomly assigned before the cutoff date (334 in the cisplatin and radiotherapy group *vs* 332 in the nivolumab,

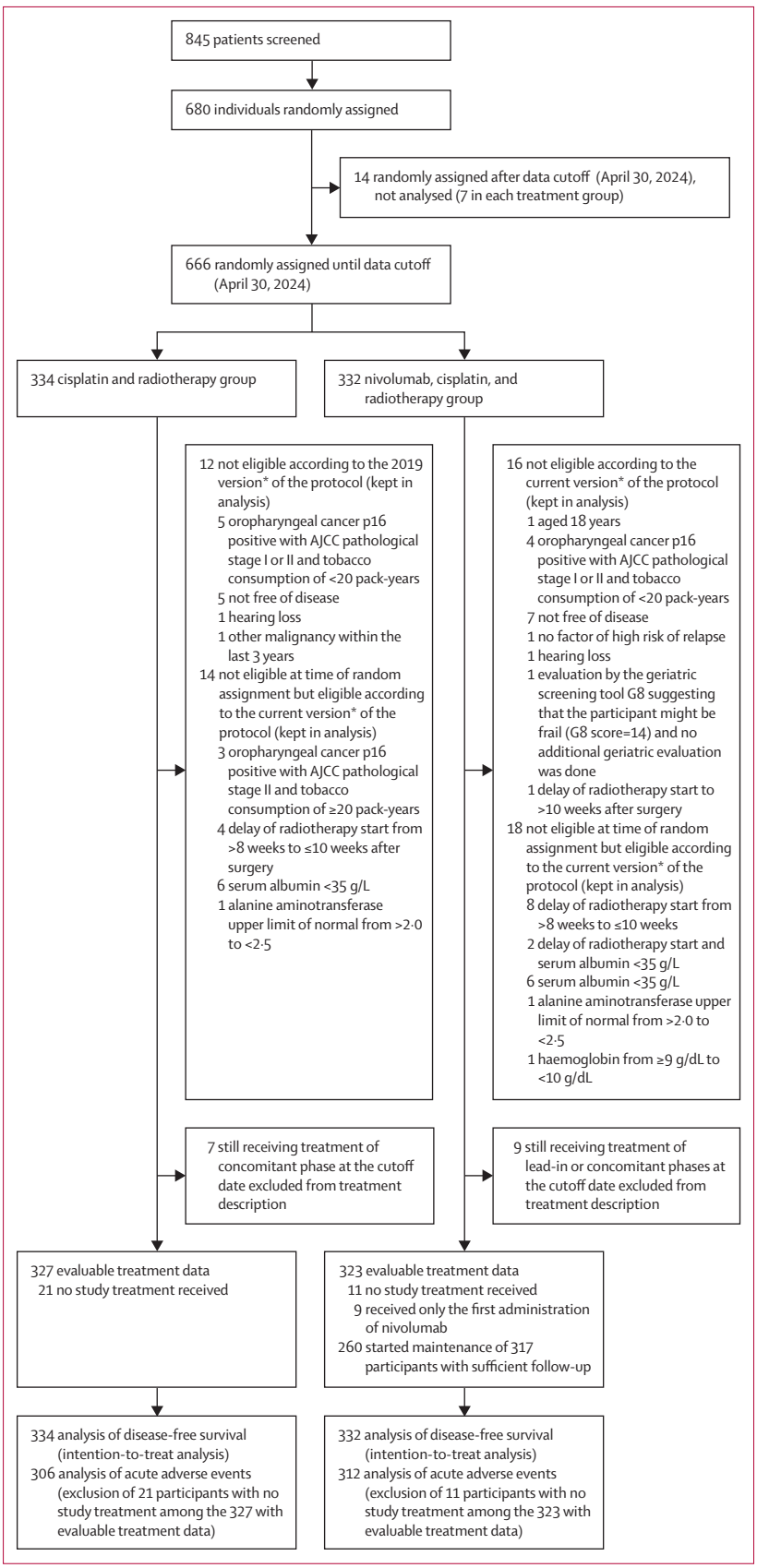


***Figure 1:*** **Trial profile**

AJCC=American Joint Committee on Cancer. *Inclusion criteria were amended in 2019, as follows: (1) addition of eligibility of pathological stage II (AJCC 8th edition) for participants with p16-positive oropharyngeal cancer with pT3N1 or pT4N1 and tobacco consumption of 20 pack-years or more; (2) modification of the criteria for ability to receive cisplatin 100 mg/m² for three cycles: haemoglobin 9 g/dL or more (instead of 10 g/dL or more), aspartate aminotransferase and alanine aminotransferase less than 2·5 times the upper limit of normal (instead of less than 2·0 times the upper limit of normal), and removal of the serum albumin condition (instead of serum albumin more than 35 g/L); and (3) an extension of the time to start radiotherapy to 10 weeks after surgery.

| | Cisplatin and radiotherapy (n=334) | Nivolumab, cisplatin, and radiotherapy (n=332) |
|---|---|---|
| **Age, years** | | |
| Median, IQR | 59 (53–64) | 59 (53–65) |
| Range | 22–74 | 18–74 |
| **Sex** | | |
| Female | 77 (23%) | 82 (25%) |
| Male | 257 (77%) | 250 (75%) |
| **Eastern Cooperative Oncology Group performance status** | | |
| 0 | 168 (50%) | 169 (51%) |
| 1 | 166 (50%) | 163 (49%) |
| **Smoking status** | | |
| Never smoked | 64 (19%) | 45 (14%) |
| Former smoker | 109 (33%) | 108 (33%) |
| Current smoker | 161 (48%) | 179 (54%) |
| **Number of pack-years in former or current smokers** | | |
| Median, IQR | 40 (25–45) | 40 (25–50) |
| Range | 1–150 | 1–150 |
| **Site of cancer and p16 status** | | |
| Oral cavity | 193 (58%) | 192 (58%) |
| Hypopharynx | 40 (12%) | 43 (13%) |
| Larynx | 41 (12%) | 40 (12%) |
| Oropharyngeal cancer p16 negative | 43 (13%) | 41 (12%) |
| Oropharyngeal cancer p16 positive | 17 (5%) | 16 (5%) |
| **Pathological stage** | | |
| I | 3 (1%) | 3 (1%) |
| II | 8 (2%) | 9 (3%) |
| III | 46 (14%) | 44 (13%) |
| IVa | 117 (35%) | 128 (39%) |
| IVb | 160 (48%) | 148 (45%) |
| **Pathological factors of a high risk of relapse*** | | |
| Node with extracapsular extension† | 213 (64%) | 205 (62%) |
| Positive margins | 183 (55%) | 203 (61%) |
| Multiple perineural invasion‡ | 188 (56%) | 182 (55%) |
| Four or more involved nodes without extracapsular extension | 44 (13%) | 42 (13%) |
| **Combination of factors of a high risk of relapse** | | |
| Extracapsular extension and positive margins | 100 (30%) | 109 (33%) |
| Extracapsular extension or positive margins | 196 (59%) | 190 (57%) |
| No extracapsular extension, no positive margins, but multiple perineural invasion or four or more involved nodes | 38 (11%) | 32 (10%) |
| No factor of high risk of relapse | 0 | 1 |
| **PD-L1 combined positive score§** | | |
| Negative | 34/308 (11%) | 44/313 (14%) |
| 1–19 | 141/308 (46%) | 157/313 (50%) |
| ≥20 | 133/308 (43%) | 113/313 (36%) |

Data are median (IQR), range, or n (%). PD-L1=programmed death ligand 1. *One participant in the nivolumab plus cisplatin plus radiotherapy group had no pathological factors of a high risk of relapse (eligibility criteria violation). †Missing in one participant of the cisplatin plus radiotherapy group. This participant had positive margins. ‡Missing in three participants: one in the cisplatin plus radiotherapy group (positive margins, nodal extracapsular extension, and more than four involved nodes) and two in the nivolumab plus cisplatin plus radiotherapy group (one had positive margins, nodal extracapsular extension, and more than four involved nodes and the other had four involved nodes, no extracapsular extension, and negative margins). §PD-L1 combined positive score was not evaluated in 44 (7%) participants: 26 (8%) in the cisplatin plus radiotherapy group and 18 (5%) in the nivolumab plus cisplatin plus radiotherapy group.

***Table 1:*** **Characteristics of the participants at baseline**

cisplatin, and radiotherapy group; figure 1) and 252 disease-free survival events. Baseline demographics and tumour, pathological, and clinical characteristics are reported in table 1. Protocol deviations are presented in the appendix (p 11).

Treatment description was based on 650 participants who passed the initial treatment phase of radiotherapy and cisplatin, with or without nivolumab, at the data cutoff date: 327 in the cisplatin and radiotherapy group and 323 in the nivolumab, cisplatin, and radiotherapy group. 21 participants in the cisplatin and radiotherapy group and 20 participants in the nivolumab, cisplatin, and radiotherapy group (6% in both groups) did not receive radiotherapy or cisplatin. The radiation dose to high-risk planning target volume was 66 Gy in 291 (89%) of 327 participants in the cisplatin and radiotherapy group and 275 (85%) of 323 participants in the nivolumab, cisplatin, and radiotherapy group. In the participants who received radiotherapy, the median time from surgery to initiation of radiotherapy was 7·7 weeks (IQR 6·6–8·6) in the cisplatin and radiotherapy group and 8·0 weeks (6·9–9·0) in the nivolumab, cisplatin, and radiotherapy group; and the radiotherapy overall duration was 55 days or fewer in 297 (97%) of 306 participants in the cisplatin and radiotherapy group and in 289 (95%) of 303 participants in the nivolumab, cisplatin, and radiotherapy group (appendix pp 12–13). At the time of publication, radiotherapy quality assurance was available for 527 participants (87% of 609 participants treated by radiotherapy before the cutoff date). High-risk planning target volume deviations (insufficient dose or volume coverage) were observed in 20 (8%) of 265 participants in the cisplatin and radiotherapy group and 19 (7%) of 262 in the nivolumab, cisplatin, and radiotherapy group.

The median cumulative dose of cisplatin was 280 mg/m² (IQR 200–300) in the cisplatin and radiotherapy group and 274 mg/m² (IQR 200–300) in the nivolumab, cisplatin, and radiotherapy group. 263 (80%) of 327 participants in the cisplatin and radiotherapy group and 248 (77%) of 323 participants in the nivolumab, cisplatin, and radiotherapy group received a total dose of cisplatin of 200 mg/m² or more. Nine participants in the cisplatin and radiotherapy group and eight in the nivolumab, cisplatin, and radiotherapy group switched to carboplatin.

In 323 participants in the nivolumab, cisplatin, and radiotherapy group evaluable for treatment description, the number of administrations of nivolumab before and during radiotherapy was three or less in 91 (28%) participants and four in 232 (72%) participants. In the nivolumab, cisplatin, and radiotherapy group, 260 (82%) of 317 participants who finished the concomitant phase at the cutoff date started maintenance. In 317 participants who finished the treatment phases, including non-treated participants (ie, those who did not receive any study treatment), the median number of

nivolumab administrations was ten (IQR 6–10). A summary of nivolumab exposure is provided in the appendix (pp 13–14).

At the data cutoff, with a median follow-up of 30·3 months (IQR 16·0–44·9), 252 participants had a disease-free survival event: 140 in the cisplatin and radiotherapy group and 112 in the nivolumab, cisplatin, and radiotherapy group. Because the required number of disease-free survival events, 230, was reached, the primary analysis of the trial was done. The number and types of first events for disease-free survival are described in table 2. Locoregional relapses were confirmed by pathological analysis in 46 (46%) of 100 participants: 29 (48%) of 61 in the cisplatin and radiotherapy group and 17 (44%) of 39 in the nivolumab, cisplatin, and radiotherapy group. The addition of nivolumab to adjuvant cisplatin and radiotherapy after surgery improved disease-free survival: the p value of the stratified log-rank test was 0·034; the HR of disease-free survival events, stratified for p16 status, was 0·76 (95% CI 0·60–0·98); and the 3-year disease-free survival was 52·5% (46·2–58·4%) in the cisplatin and radiotherapy group versus 63·1% (57·0–68·7%) in the nivolumab, cisplatin, and radiotherapy group (figure 2). There was no evidence of violation of the proportional hazards assumption. The improvement in disease-free survival was mainly due to a reduction in the incidence of locoregional relapses with a stratified subdistribution HR of 0·63 (0·42–0·94; table 2 and appendix pp 15–16).

158 participants died (86 in the cisplatin and radiotherapy group and 72 in the nivolumab, cisplatin, and radiotherapy group; appendix p 17). The statistical analysis of overall survival requires more mature data and will be performed when the prespecified number of deaths is reached.

Figure 3 presents subgroup analyses of disease-free survival. No significant interaction with treatment was found and all HRs of disease-free survival events were in favour of nivolumab, cisplatin, and radiotherapy (ie, HR less than 1), except for participants with laryngeal tumour or p16-positive oropharyngeal cancer. However, these two subgroups were very small. PD-L1 combined positive score was not a good predictive biomarker of efficacy (figure 3; appendix p 18).

Regarding disease-free survival by masked independent central review (appendix pp 19–20), 251 participants had a disease-free survival event: 131 in the cisplatin and radiotherapy group and 120 in the nivolumab, cisplatin, and radiotherapy group. The adjusted HR was 0·89 (95% CI 0·69–1·14). The sensitivity analysis of disease-free survival by masked independent central review added 22 relapses missed by masked independent central review but confirmed by pathology (because seven participants died, 15 events were added) and removed ten events in participants who were free of disease without any oncological treatment 18–57 months after lesion identification by masked independent central review.

| | Cisplatin and radiotherapy (n=334) | Nivolumab, cisplatin, and radiotherapy (n=332) |
|---|---|---|
| Number of participants with disease-free survival event | 140 | 112 |
| Type of first event | | |
| Local relapse alone | 30 | 15 |
| Regional relapse alone | 20 | 12 |
| Locoregional relapse | 11 | 12 |
| Distant relapse alone | 40 | 37 |
| Combined locoregional and distant relapse | 22 | 16 |
| Death as first event | 17 | 20 |
| Disease-free survival | | |
| 3-year rate | 52·5% (46·2–58·4) | 63·1% (57·0–68·7) |
| Stratified* HR of disease-free survival event | 1 | 0·76 (0·60–0·98) |
| Cumulative incidence of locoregional relapse alone | | |
| 3-year rate | 19·8% (15·3–24·6) | 12·9% (9·3–17·2) |
| Stratified* subdistribution HR of locoregional relapse alone | 1 | 0·63 (0·42–0·94) |
| Cumulative incidence of distant relapse alone | | |
| 3-year rate | 13·2% (9·6–17·5) | 12·6% (9·0–16·8) |
| Stratified* subdistribution HR of distant relapse alone | 1 | 0·95 (0·61–1·48) |
| Cumulative incidence of combined locoregional and distant relapse | | |
| 3-year rate | 7·6% (4·9–11·1) | 5·7% (3·4–8·8) |
| Stratified* subdistribution HR of locoregional and distant relapse | 1 | 0·74 (0·39–1·41) |
| Cumulative incidence of death as first event | | |
| 3-year rate | 6·9% (4·1–10·7) | 5·7% (3·3–9·0) |
| Stratified* subdistribution HR of death as first event | 1 | 1·20 (0·63–2·28) |

Data are n, rate (95% CI), or HR (95% CI). HR=hazard ratio. *Stratified for p16 status (oropharyngeal cancer p16 positive *vs* oropharyngeal cancer p16 negative and non-oropharyngeal cancer).

***Table 2:*** **Disease-free survival analysis**

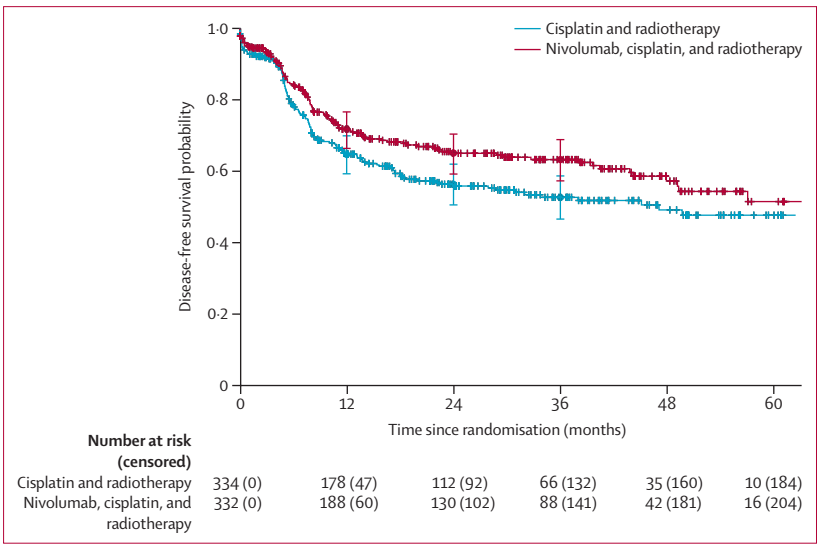


***Figure 2:*** **Kaplan–Meier estimates of disease-free survival according to treatment group**

| | Cisplatin and radiotherapy | | Nivolumab, cisplatin, and radiotherapy | | Crude HR (95% CI) | Stratified* HR (95% CI) |
|---|---|---|---|---|---|---|
| | n | Events | n | Events | | |
| **Age (years)** | | | | | | |
| <65 | 266 | 113 | 249 | 82 | 0·71 (0·54–0·95) | 0·71 (0·54–0·95) |
| ≥65 | 68 | 27 | 83 | 30 | 0·95 (0·56–1·59) | 0·95 (0·56–1·61) |
| **Sex** | | | | | | |
| Female | 77 | 28 | 82 | 28 | 0·88 (0·52–1·49) | 0·88 (0·52–1·49) |
| Male | 257 | 112 | 250 | 84 | 0·74 (0·56–0·98) | 0·74 (0·56–0·98) |
| **Smoking status** | | | | | | |
| Current smoker | 161 | 70 | 179 | 61 | 0·72 (0·51–1·02) | 0·72 (0·51–1·02) |
| Former smoker | 109 | 47 | 108 | 38 | 0·80 (0·52–1·22) | 0·77 (0·50–1·18) |
| Never smoker | 64 | 23 | 45 | 13 | 0·82 (0·41–1·61) | 0·77 (0·39–1·52) |
| **Alcohol consumption** | | | | | | |
| Current | 83 | 36 | 87 | 21 | 0·53 (0·31–0·90) | 0·51 (0·30–0·87) |
| Former | 141 | 62 | 150 | 62 | 0·92 (0·64–1·30) | 0·92 (0·65–1·31) |
| Never | 110 | 42 | 95 | 29 | 0·76 (0·48–1·23) | 0·76 (0·47–1·22) |
| **Performance score** | | | | | | |
| Eastern Cooperative Oncology Group 0 | 168 | 60 | 169 | 46 | 0·76 (0·52–1·12) | 0·76 (0·52–1·12) |
| Eastern Cooperative Oncology Group 1 | 166 | 80 | 163 | 66 | 0·75 (0·54–1·04) | 0·75 (0·54–1·05) |
| **Haemoglobin** | | | | | | |
| <lower limit of normal | 195 | 88 | 201 | 76 | 0·75 (0·56–1·03) | 0·75 (0·55–1·02) |
| ≥lower limit of normal | 139 | 52 | 131 | 36 | 0·76 (0·49–1·16) | 0·76 (0·49–1·16) |
| **Tumour site** | | | | | | |
| Hypopharynx | 40 | 24 | 43 | 13 | 0·44 (0·22–0·88) | 0·44 (0·22–0·88) |
| Larynx | 41 | 17 | 40 | 15 | 1·00 (0·50–2·00) | 1·00 (0·50–2·00) |
| Oropharynx | 60 | 24 | 57 | 24 | 0·97 (0·55–1·71) | 0·94 (0·53–1·66) |
| Oral cavity | 193 | 75 | 192 | 60 | 0·75 (0·54–1·06) | 0·75 (0·53–1·05) |
| **Site and p16 status** | | | | | | |
| Non-oropharyngeal cancer | 274 | 116 | 275 | 88 | 0·73 (0·55–0·96) | .. |
| Oropharyngeal cancer p16 negative | 43 | 18 | 41 | 18 | 0·87 (0·45–1·70) | .. |
| Oropharyngeal cancer p16 positive | 17 | 6 | 16 | 6 | 1·13 (0·36–3·51) | .. |
| **Pathological stage** | | | | | | |
| I–III | 57 | 17 | 56 | 14 | 0·81 (0·40–1·64) | 0·81 (0·40–1·64) |
| IV | 277 | 123 | 276 | 98 | 0·76 (0·58–0·99) | 0·76 (0·58–0·99) |
| **PD-L1 combined positive score** | | | | | | |
| <1 | 34 | 14 | 44 | 16 | 0·92 (0·45–1·88) | 0·85 (0·42–1·75) |
| ≥1 to <20 | 141 | 69 | 157 | 57 | 0·65 (0·46–0·92) | 0·64 (0·45–0·91) |
| ≥20 | 133 | 45 | 113 | 35 | 0·91 (0·58–1·41) | 0·88 (0·56–1·37) |
| Unknown | 26 | 12 | 18 | 4 | 0·59 (0·19–1·83) | 0·59 (0·19–1·83) |
| **Multiple perineural invasion** | | | | | | |
| No | 145 | 57 | 148 | 50 | 0·88 (0·60–1·29) | 0·88 (0·60–1·28) |
| Yes | 188 | 83 | 182 | 61 | 0·67 (0·48–0·94) | 0·67 (0·48–0·94) |
| **Number of involved nodes without extracapsular extension** | | | | | | |
| <4 | 290 | 113 | 290 | 90 | 0·75 (0·57–0·99) | 0·75 (0·57–0·99) |
| ≥4 | 44 | 27 | 42 | 22 | 0·89 (0·50–1·56) | 0·78 (0·44–1·38) |
| **Nodal extracapsular extension** | | | | | | |
| No | 120 | 39 | 127 | 30 | 0·64 (0·40–1·04) | 0·64 (0·40–1·03) |
| Yes | 213 | 100 | 205 | 82 | 0·85 (0·64–1·14) | 0·85 (0·64–1·14) |
| **Positive margins** | | | | | | |
| No | 151 | 62 | 129 | 39 | 0·68 (0·46–1·02) | 0·68 (0·45–1·02) |
| Yes | 183 | 78 | 203 | 73 | 0·83 (0·60–1·14) | 0·82 (0·60–1·13) |
| **All patients** | **334** | **140** | **332** | **112** | **0·77 (0·60–0·98)** | **0·76 (0·60–0·98)** |

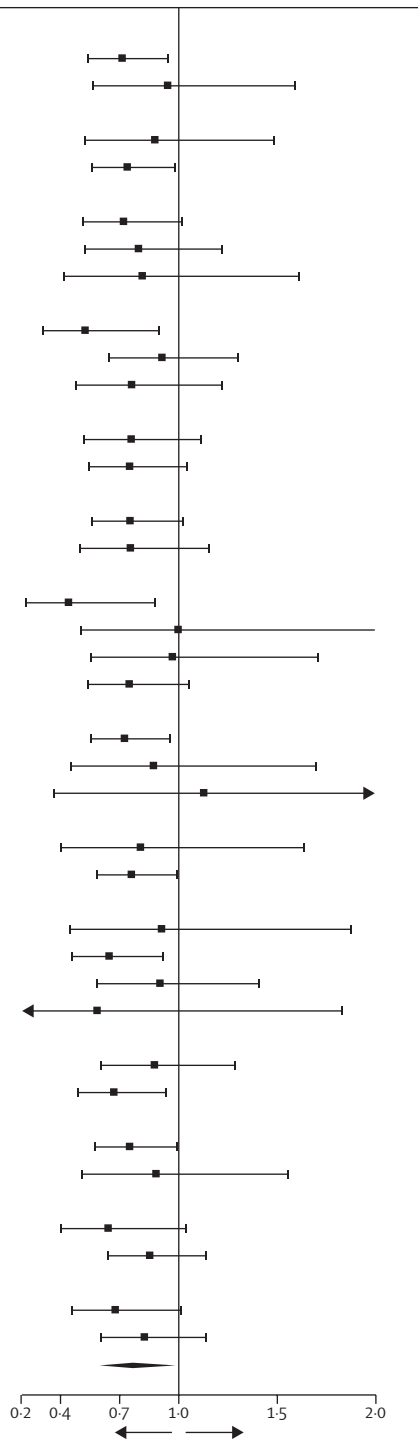


***Figure 3:*** **Subgroup analysis of disease-free survival**
Crude HRs are represented in the forest plot. *HRs are stratified for p16 status (p16-positive oropharyngeal cancer *vs* p16-negative oropharyngeal cancer and non-oropharyngeal cancer). HR=hazard ratio. PD-L1=programmed death ligand 1.

There were then 138 events in the cisplatin and radiotherapy group and 118 in the nivolumab, cisplatin, and radiotherapy group, and the adjusted HR was 0·81 (0·63–1·03).

The independent data monitoring committee reviewed safety reports when 20 participants who had finished the cisplatin and radiotherapy (with or without nivolumab) treatment phase, and when 121 and 241 participants had received at least one dose of treatment and were followed up for 9 months, and recommended the trial to continue after each of its assessments. Among treated participants (306 in the cisplatin and radiotherapy group, 312 in the nivolumab, cisplatin, and radiotherapy group; figure 1), over the three safety periods, grade 5 adverse events were observed only in the two first periods (up to 100 days after the last treatment of lead-in and concomitant phases and between 101 days and 9 months after the last treatment of lead-in and concomitant phases) in ten (3%) participants in the cisplatin and radiotherapy group (four in the first period and six in the second period), including two treatment-related deaths (1%; a participant died of acute respiratory syndrome, kidney injury, and sepsis; and the other died of infection), and in eight (3%) participants in the nivolumab, cisplatin, and radiotherapy group (seven in the first period and one in the second period), also including two treatment-related deaths (1%; a participant died of acute kidney injury and pancytopenia, and the other died of aspiration pneumonia). Grade 5 adverse events are described in the appendix (p 23).

227 (73%) of 312 participants in the nivolumab, cisplatin, and radiotherapy group versus 209 (68%) of 306 participants in the cisplatin and radiotherapy group had at least one grade 3 treatment-related adverse event and 30 (10%) participants in the nivolumab, cisplatin, and radiotherapy group versus 16 (5%) participants in the cisplatin and radiotherapy group had at least one grade 4 treatment-related adverse event (table 3). Treatment-related serious adverse events were reported in 104 (33%) of 312 participants in the nivolumab, cisplatin, and radiotherapy group and in 59 (19%) of 306 participants in the cisplatin and radiotherapy group (table 3). The most common treatment-related adverse events of any grade (occurring in >20% of all participants) during the two first periods were those expected in participants treated by cisplatin and radiotherapy: stomatitis (512 [83%] of 618 participants), radiation skin injury (425 [69%]), dysphagia (332 [54%]), nausea (290 [47%]), dry mouth (263 [43%]), dysgueusia (252 [41%]), asthenia (247 [40%]), neutropenia (202 [33%]), anaemia (190 [31%]), and tinnitus (132 [21%]; appendix p 33). During these two first periods, some treatment-related adverse events were more frequent or more severe in the nivolumab, cisplatin, and radiotherapy group than in the cisplatin and radiotherapy group, including: thyroid disorders (63 [20%] of 312 *vs* seven [2%] of 306; only grade 1 or 2 adverse events), any grade renal disorders (74 [24%] *vs* 46 [15%]), and grade 3–4 dysphagia (75 [24%] *vs* 54 [18%]; appendix p 34). All treatment-related adverse events occurring during the two first periods are presented in the appendix (pp 24–47).

Details of nivolumab-related adverse events and serious adverse events occurring during the two first periods are in the appendix (pp 48–53). The most common nivolumab-related adverse events were thyroid disorders (58 [19%] of 312 participants), asthenia (48 [15%]), and diarrhoea (31 [10%]).

| | Cisplatin and radiotherapy (n=306) | | | | | Nivolumab, cisplatin, and radiotherapy (n=312) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Any grade | Grade 3–5 | Grade 3 | Grade 4 | Grade 5 | Any grade | Grade 3–5 | Grade 3 | Grade 4 | Grade 5 |
| **Treatment-related adverse events** | | | | | | | | | | |
| Any | 304 (99%) | 211 (69%) | 209 (68%) | 16 (5%) | 2 (1%) | 301 (96%) | 230 (74%) | 227 (73%) | 30 (10%) | 2 (1%) |
| Serious | 59 (19%) | 48 (16%) | 45 (15%) | 4 (1%) | 2 (1%) | 104 (33%) | 91 (29%) | 84 (27%) | 14 (4%) | 2 (1%) |
| **Nivolumab-related adverse events** | | | | | | | | | | |
| Any | NA | NA | NA | NA | NA | 213 (68%) | 64 (21%) | 58 (19%) | 6 (2%) | 2 (1%) |
| Leading to nivolumab discontinuation | NA | NA | NA | NA | NA | 25 (8%) | 14 (4%) | 12 (4%) | 2 (1%) | 0 |
| Serious | NA | NA | NA | NA | NA | 32 (10%) | 25 (8%) | 21 (7%) | 3 (1%) | 2 (1%) |
| **Cisplatin-related adverse events** | | | | | | | | | | |
| Any | 291 (95%) | 157 (51%) | 154 (50%) | 16 (5%) | 2 (1%) | 286 (92%) | 176 (56%) | 168 (54%) | 27 (9%) | 1 (<1%) |
| Leading to cisplatin discontinuation | 54 (18%) | 37 (12%) | 34 (11%) | 4 (1%) | 0 | 65 (21%) | 49 (16%) | 41 (13%) | 10 (3%) | 0 |
| Serious | 54 (18%) | 44 (14%) | 41 (13%) | 4 (1%) | 2 (1%) | 75 (24%) | 68 (22%) | 58 (19%) | 13 (4%) | 1 (<1%) |
| **Radiotherapy-related adverse events** | | | | | | | | | | |
| Any | 297 (97%) | 156 (51%) | 156 (51%) | 2 (1%) | 0 | 294 (94%) | 161 (52%) | 159 (51%) | 9 (3%) | 0 |
| Serious | 18 (6%) | 12 (4%) | 12 (4%) | 1 (<1%) | 0 | 39 (13%) | 30 (10%) | 28 (9%) | 4 (1%) | 0 |

Since the same adverse events can be related to several treatments (nivolumab, cisplatin, and radiotherapy), the number of participants with treatment-related adverse events is not the sum of participants with adverse events related to nivolumab, cisplatin, and radiotherapy. N/A=not applicable.

***Table 3:*** **Number of participants with adverse events and serious adverse events (all periods together)**

After 9 months (the third safety period), 235 participants in the cisplatin and radiotherapy group and 234 in the nivolumab, cisplatin, and radiotherapy group were evaluable for safety. With the current follow-up, nine (4%) participants in the cisplatin and radiotherapy group and ten (4%) participants in the nivolumab, cisplatin, and radiotherapy group had grade 3 treatment-related adverse events (appendix p 55). No participant had a grade 4 treatment-related adverse event. The most common adverse events were those expected after concomitant radiochemotherapy: dry mouth, dysphagia, radiation fibrosis, and dysgeusia (appendix p 57). Treatment-related adverse events occurring during the third period are presented in the appendix (pp 55–60).

42 participants had a second primary malignancy (the most common were lung cancers [n=15], followed by colorectal [n=5], liver [n=4], and prostate cancers [n=4]): 24 in the cisplatin and radiotherapy group and 18 in the nivolumab, cisplatin, and radiotherapy group. The 3-year rate of second primary malignancy was 10·7% (95% CI 6·8–16·5) in the cisplatin and radiotherapy group and 8·8% (5·3–14·5) in the nivolumab, cisplatin, and radiotherapy group (appendix p 21).

## Discussion

The study met its primary objective of increasing disease-free survival when adding nivolumab to the standard-of-care cisplatin and radiotherapy compared with cisplatin and radiotherapy alone in participants with resected LA-SCCHN at a high risk of relapse, mainly by reducing locoregional relapses. This benefit was observed irrespective of PD-L1 expression.

There was some discrepancy between disease-free survival when assessed by masked independent central review versus assessed by investigator. Both endpoints might have been affected by errors. Due to the absence of masking, there was a risk of bias in investigator-assessed disease-free survival. To limit this risk, the NIVOPOST-OP protocol imposed a rigorous schedule of clinical and imaging oncological assessments, regularly verified during on-site monitoring. However, masked independent central review, as performed in NIVOPOST-OP (ie, based solely on imaging, without any knowledge of clinical and pathological information) presented some limitations. In resected LA-SCCHN, postoperative and postradiation changes, including fibrosis, flap reconstruction, and inflammation, might complicate the imaging assessment, making it challenging to distinguish post-therapeutic scarring or inflammation from recurrent disease. Consequently, the masked independent central review resulted in 22 false negative cases, where biopsies confirmed relapse despite negative masked independent central review findings, and ten false positive cases, where masked independent central review indicated relapse not substantiated by long-term follow-up without further oncological treatment. The sensitivity analysis accounting for these 32 tangible misclassifications showed an HR of 0·81, closer to the HR for investigator-assessed events, although the upper bound of its 95% CI was 1·03. The difference between these two HRs was of the same order of magnitude as that between the HR for investigator-assessed events and that for central review-assessed events observed in a large-scale lapatinib randomised trial,[9] which was a double-blind trial where central review was based both on imaging and clinical, pathological, and endoscopic information.

Overall survival results (appendix p 17) appeared consistent with the disease-free survival improvement, but the study is not mature for testing overall survival since the number of deaths required for analysis has not been reached. In LA-SCCHN, disease-free survival generally appears as a good surrogate for overall survival,[17] but overall survival events are markedly delayed since the median overall survival of people with recurrent or metastatic SCCHN is at least 13 months.[11,18] Disease-free survival appears to be a clinically meaningful endpoint for people with resected LA-SCCHN disease, since the large majority of the relapses are not amenable to any curative approach.[1–3,8–11] Notably, the number of participants receiving PD-1 blockade at relapse was markedly different between the two groups (appendix p 22). The potential effect of delayed versus early PD-1 blockade is not known in LA-SCCHN. However, early intervention by reducing the relapse rate might be more impactful on the final outcome of participants.

The benefit observed on locoregional relapses and disease-free survival was at the price of a moderate increase in toxic effects. There was a moderate increase of participants with grade 3 treatment-related adverse events (73% *vs* 68%) and grade 4 treatment-related adverse events (10% *vs* 5%), mainly during the treatment periods. There was a slight increase of renal adverse events in the nivolumab group. Although cisplatin is notorious for its nephrotoxic effects, anti-PD-1 inhibitors can also cause nephritis. Combining these two drugs might increase the risk of renal toxic effects[19] and close monitoring of kidney function is essential to ensure patient safety. It is essential to note that there was no increase in treatment-related deaths (two in each group) nor in the long-term toxic effects.

This large-scale phase 3 trial shows the superiority of the addition of nivolumab over the standard-of-care cisplatin and radiotherapy alone, which was established more than 20 years ago.[2,3,8] Since then, attempts to improve this standard cisplatin and radiotherapy have failed both in people treated either primarily by surgery[1,9] or primarily by radiotherapy,[12,13] and the relatively poor outcome seen in our standard-of-care group with a 52·5% rate of disease-free survival at 3 years is in the range of those previously reported[1–3,8,9] in large-scale randomised studies using adjuvant chemoradiotherapy in people who had undergone an operation, pointing out

the persistent unmet clinical need for this LA-SCCHN population at a high risk. The benefit of adding nivolumab to cisplatin and radiotherapy (with an HR of disease-free survival events of 0·76; an increase of 10·6% in the 3-year disease-free survival rate) is comparable to that of having added concomitant chemotherapy to radiotherapy, which defined the standard of care 20 years ago (HR 0·78; increase of 9% in the 3-year event-free survival rate).[20]

One of the limitations of our study is the small number of patients with p16-positive oropharyngeal SCC, which does not allow for the evaluation of the effect of nivolumab in this particular population. Another potential limitation is related to the unmasked design. In addition to the rigorous oncological assessment schedule aimed at limiting bias related to the investigator-based assessment of relapses, the protocol detailed treatment modification methods to limit differences in management between investigators, adverse events were evaluated using standardised criteria (National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0), and on-site monitoring of protocol adherence and all case report form variables of all participants was performed.

PD-1 blockade is established as the standard of care in recurrent or metastatic SCCHN,[10,11] but in contrast, several phase 2–3 randomised trials (KEYNOTE-412,[13] GORTEC 2015–01 PembroRad,[15] GORTEC 2017–01 REACH,[16] IMvoke010,[14] and JAVELIN Head and Neck 100[12]) did not show a benefit of PD-1 and PD-L1 blockade in the definitive treatment of unresected or unresectable LA-SCCHN. Based on the PD-L1 subgroup analyses of these trials, it is unclear whether the benefit was more pronounced when high expression of PD-L1 was present, which has been inconsistent among trials.[12–16] Aligned with these observations, in our trial, the benefit was observed in all participants for whom the PD-L1 combined positive score was known, and combined positive score was not a good predictive biomarker of the efficacy of nivolumab.

In contrast with the trials performed in people with unresected or unresectable LA-SCCHN, which did not meet their efficacy endpoints, a recent large-scale randomised KEYNOTE-689 study[21] showed a benefit associated with pembrolizumab given in the perioperative setting. Despite showing similar outcomes on their primary endpoints—namely, event-free survival (in the KEYNOTE-689 study) and disease-free survival (in our NIVOPOST-OP study)—there were several important differences between the two studies. In the KEYNOTE-689 study, selection was based on people with resectable disease (they were not all operated on), and there were no high-risk features in 42% of participants in the control group. In contrast, the selection in NIVOPOST-OP was based on people with resected disease, all with a high risk of relapse (only 11% without the high-risk features that were considered in the KEYNOTE-689 study). The duration of exposure to anti-PD-1 was longer in the KEYNOTE-689 study (median duration, 0·7 months in the neoadjuvant phase and 9·7 months in the concomitant and adjuvant phases) than in the NIVOPOST-OP study (7·4 months in the concomitant and adjuvant phases) and the observed benefit was also different on distant metastases for the KEYNOTE-689 study and on locoregional relapses for NIVOPOST-OP study. Finally, it is difficult in both studies to understand the contribution of individual components, since the KEYNOTE-689 study had neoadjuvant, concomitant with radiotherapy, and adjuvant components, whereas the NIVOPOST-OP study had concomitant and adjuvant phases. Despite these differences, the results of both the NIVOPOST-OP and the KEYNOTE-689 studies suggest that PD-1 blockade could be more efficient in the perioperative setting of resectable LA-SCCHN compared with the unresected or unresectable setting with bulky tumours in place, although PD-1 blockade has shown efficacy in the recurrent or metastatic setting.[11]

In summary, the NIVOPOST-OP trial establishes the proof of principle that postoperative nivolumab added to standard-of-care cisplatin and radiotherapy is a way to improve patient outcomes for resected high-risk LA-SCCHN, and could be proposed as a new standard treatment.

#### Contributors

All authors had full access to the data, vouch for their accuracy, and attest that the study conformed to the protocol. AA and EK analysed the data, which were subsequently interpreted by all authors. All authors contributed to the reviewing and amending of the manuscript. The corresponding authors (YT and JB) had the final responsibility to submit the publication. JB, AA, and YT had full access to all the data in the study and verified the data and take responsibility for the integrity of the data and the accuracy of the data analysis.

#### Declaration of interests

JB reports participation on an advisory board for MSD, Bristol Myers Squibb, Nanobiotix, Merck, Astra, Transgene, and Roche. AA reports grants from GORTEC during the conduct of the study and has been an advisory member for MSD outside of the submitted work, all paid to her institution. CB reports consulting fees from MSD, Bristol Myers Squibb, and Merck; honoraria from MSD; travel fees from MSD and Merck; and participation on a data safety monitoring board or advisory board for MSD, Bristol Myers Squibb, and Merck. XSS reports travel fees from Merck. ES reports grants or contracts from INCa, ARC, AstraZeneca, and Merck Serono; consulting fees from Merck Serono, AstraZeneca, and MSD; honoraria for lectures from Merck Serono and MSD; support for attending meetings and travel from Merck Serono, MSD, and Novartis; and travel fees from MSD and Merck Novartis. BCi reports honoraria from MSD, Bristol Myers Squibb, Merck, Pierre-Fabre, and Pfizer; payment for expert testimony from MSD, Bristol Myers Squibb, and Merck; and travel fees from MSD, Bristol Myers Squibb, and Merck. TR reports a grant for implementation of clinical trials with immunotherapy including this current trial. MBa reports financial grants by Gilead and AstraZeneca; and travel support from Merck. STh reports a grant from INCa; and travel fees from Merck. YP reports consulting fees and advisory board participation from Bristol Myers Squibb and MSD; and symposium honoraria from Bristol Myers Squibb, MSD, Merck, and J&J. PB reports payment or honoraria for lectures (to institution) from MSD. SL reports support for attending meetings from Merck Serono. JV reports travel support from Merck. MP reports travel support from Eisai Europe. STe reports consulting fees from MSD to their institution. CE reports consulting fees from MSD, Merck, GSK,

PDS Biotechnology, Novartis, Bicara, Merus, Elevar, Leo Pharma, and Bristol Myers Squibb; and travel support from MSD and Merck. JT reports institutional honoraria from Bristol Myers Squibb and Neolys ALARA; and travel and accommodation expenses from Nanobiotix and Merck. JK reports honoraria for lectures from MSD. AP reports a grant from Bristol Myers Squibb to their institution; and personal consulting fees and honoraria for lectures from Bristol Myers Squibb. YT reports consulting fees from MSD and Merck; honoraria from MSD and Seagen; and travel support from MSD and Merck. All other authors declare no competing interests.

### Data sharing

The study protocol and the statistical analysis plan are available at the end of the appendix. Individual patient data, including data dictionaries, will be available after the publication of the overall survival analysis. Qualified researchers should submit a request to jean.bourhis@gortec.fr. A document indicating the objective of the research, the methods, the statistical analysis plan, and the variables within the database required for the research must be submitted. The GORTEC scientific board will review and approve the request. If the request is approved, the data required for the research will be shared. A specific agreement between GORTEC and the researcher will be requested for data transfer, detailing both parties' responsibilities to ensure the required level of data integrity along with legal and ethical obligations.

### Acknowledgments

We are indebted to the following, without whose support this work would not have been possible: the people who volunteered to participate in this trial; the physicians, nurses, research associates, and staff members of the GORTEC headquarters, Gaëtan Osne, Solène Jamet, Caroline Cendrier, Jean Pierre Pignon, Sarah Jorge, and the GORTEC operational team who assisted in providing care and safeguarding the validity of the collected data. We thank GORTEC, the Spanish Head and Neck Oncology Group (in particular Carmen Montalbán), the Hellenic Oncology Group, and trial endorsement by the Head and Neck Cancer International Group. This study was funded by GORTEC and Bristol Myers Squibb. We thank the members of the independent data monitoring committee: René Leemans, Esat Mahmut Ozsahin, Simon Thezenas, and Jan B Vermorken.

### References

1 Pignon JP, le Maître A, Maillard E, Bourhis J. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): an update on 93 randomised trials and 17,346 patients. *Radiother Oncol* 2009; **92:** 4–14.

2 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.

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 National Comprehensive Cancer Network. NCCN Guidelines, head and neck cancers. https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1437 (accessed Dec 1, 2024).

5 Machiels JP, René Leemans C, Golusinski W, Grau C, Licitra L, Gregoire V. 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.

6 Aivazian K, Ebrahimi A, Low TH, et al. Perineural invasion in oral squamous cell carcinoma: quantitative subcategorisation of perineural invasion and prognostication. *J Surg Oncol* 2015; **111:** 352–58.

7 Ebrahimi A, Gil Z, Amit M, et al. The prognosis of N2b and N2c lymph node disease in oral squamous cell carcinoma is determined by the number of metastatic lymph nodes rather than laterality: evidence to support a revision of the American Joint Committee on Cancer staging system. *Cancer* 2014; **120:** 1968–74.

8 Pignon JP, Bourhis J, Domenge C, Designé L. Chemotherapy added to locoregional treatment for head and neck squamous-cell carcinoma: three meta-analyses of updated individual data. *Lancet* 2000; **355:** 949–55.

9 Harrington K, Temam S, Mehanna H, et al. Postoperative adjuvant lapatinib and concurrent chemoradiotherapy followed by maintenance lapatinib monotherapy in high-risk patients with resected squamous cell carcinoma of the head and neck: a phase III, randomized, double-blind, placebo-controlled study. *J Clin Oncol* 2015; **33:** 4202–09.

10 Ferris RL, Blumenschein G Jr, Fayette J, et al. Nivolumab for recurrent squamous-cell carcinoma of the head and neck. *N Engl J Med* 2016; **375:** 1856–67.

11 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.

12 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.

13 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.

14 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.

15 Tao Y, Biau J, Sun X, 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.

16 Bourhis J, Tao Y, Sun X, et al. LBA35 Avelumab-cetuximab-radiotherapy versus standards of care in patients with locally advanced squamous cell carcinoma of head and neck (LA-SCCHN): randomized phase III GORTEC-REACH trial. *Ann Oncol* 2021; **32** (suppl)**:** S1310.

17 Michiels S, Le Maître A, Buyse M, et al. Surrogate endpoints for overall survival in locally advanced head and neck cancer: meta-analyses of individual patient data. *Lancet Oncol* 2009; **10:** 341–50.

18 Guigay J, Aupérin A, Fayette J, et al. Cetuximab, docetaxel, and cisplatin versus platinum, fluorouracil, and cetuximab as first-line treatment in patients with recurrent or metastatic head and neck squamous-cell carcinoma (GORTEC 2014-01 TPExtreme): a multicentre, open-label, randomised, phase 2 trial. *Lancet Oncol* 2021; **22:** 463–75.

19 Gandhi L, Rodríguez-Abreu D, Gadgeel S, et al. Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. *N Engl J Med* 2018; **378:** 2078–92.

20 Dauzier E, Lacas B, Blanchard P, et al. Role of chemotherapy in 5000 patients with head and neck cancer treated by curative surgery: a subgroup analysis of the meta-analysis of chemotherapy in head and neck cancer. *Oral Oncol* 2019; **95:** 106–14.

21 Uppaluri R, Haddad RI, Tao Y, et al. Neoadjuvant and adjuvant pembrolizumab in locally advanced head and neck cancer. *N Engl J Med* 2025; **393:** 37–50.