Title

Safety of Nivolumab Added to Chemoradiation Therapy Platforms for Intermediate and High-Risk Locoregionally Advanced Head and Neck Squamous Cell Carcinoma: RTOG Foundation 3504

Journal

International Journal of Radiation Oncology • Biology • Physics, 115(4)

ISSN

0360-3016

Authors

Gillison, Maura L
Ferris, Robert L
Harris, Jonathan
et al.

Publication Date

2023-03-01

DOI

10.1016/j.ijrobp.2022.10.008

Peer reviewed

Published in final edited form as:

Int J Radiat Oncol Biol Phys. 2023 March 15; 115(4): 847–860. doi:10.1016/j.ijrobp.2022.10.008.

Safety of Nivolumab Added to Chemoradiation Therapy Platforms for Intermediate and High-Risk Locoregionally Advanced Head and Neck Squamous Cell Carcinoma: RTOG Foundation 3504

Maura L. Gillison, MD, PhD[*], **Robert L. Ferris, MD, PhD**[†], **Jonathan Harris, MS**[‡], **A. Dimitrios Colevas, MD**[§], **Loren K. Mell, MD**[‖], **Christina Kong, MD**[§], **Richard C. Jordan, DDS, PhD**[#], **Kevin L. Moore, PhD**[‖], **Minh-Tam Truong, MD**[**], **Claudia Kirsch, MD**[††], **Arnab Chakravarti, MD**[‡‡], **Dukagjin M. Blakaj, MD, PhD**[‡‡], **David A. Clump, MD**[†], **James P. Ohr, MD**[†], **John F. Deeken, MD**[§§], **Michael F. Gensheimer, MD**[§], **Nabil F. Saba, MD**[‖‖], **Jennifer A. Dorth, MD**[##], **David I. Rosenthal, MD**[*], **Rom S. Leidner, MD**[***], **Randall J. Kimple, MD, PhD**[†††], **Mitchell Machtay, MD**[‡‡‡], **Walter J. Curran Jr., MD**[§§§], **Pedro Torres-Saavedra, PhD**[‡], **Quynh Thu Le, MD**[§]

[*]MD Anderson Cancer Center, Houston, Texas

[†]UPMC Hillman Cancer Center, Pittsburgh, Pennsylvania

[‡]RTOG Foundation Statistics and Data Management Center, American College of Radiology, Philadelphia, Pennsylvania

[§]Stanford Cancer Institute, Palo Alto, Stanford, California

[‖]UC San Diego Moores Cancer Center, La Jolla, California

[#]UCSF Medical Center-Mount Zion, San Francisco, California

[**]Boston Medical Center, Boston, Massachusetts

[††]Yale School of Medicine, New Haven, Connecticut

[‡‡]Ohio State University Comprehensive Cancer Center, Columbus, Ohio

[§§]Inova Fairfax Hospital, Fairfax, Virginia

[‖‖]Emory University Hospital/Winship Cancer Institute, Atlanta, Georgia

[##]Case Western Reserve University, Cleveland, Ohio

[***]Providence Portland Medical Center, Portland, Oregon

[†††]University of Wisconsin Carbone Cancer Center, Madison, Wisconsin

[‡‡‡]Penn State Milton S Hershey Medical Center, Hershey, Pennsylvania

[§§§]GenesisCare, Atlanta, Georgia

Corresponding author: Quynh Thu Le, MD; Qle@stanford.edu.

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijrobp.2022.10.008.

Abstract

Purpose: Programmed death-1 immune checkpoint blockade improves survival of patients with recurrent/metastatic head and neck squamous cell carcinoma (HNSCC), but the benefits of addition to (chemo)radiation for newly diagnosed patients with HNSCC remain unknown.

Methods and Materials: We evaluated the safety of nivolumab concomitant with 70 Gy intensity modulated radiation therapy and weekly cisplatin (arm 1), every 3-week cisplatin (arm 2), cetuximab (arm 3), or alone for platinum-ineligible patients (arm 4) in newly diagnosed intermediate- or high-risk locoregionally advanced HNSCC. Patients received nivolumab from 2 weeks prior to radiation therapy until 3 months post-radiation therapy. The primary endpoint was dose-limiting toxicity (DLT). If ≤2 of the first 8 evaluable patients experienced a DLT, an arm was considered safe. Secondary endpoints included toxicity and feasibility of adjuvant nivolumab to 1 year, defined as all 7 additional doses received by ≥4 of the first 8 evaluable patients across arms.

Results: Of 39 patients (10 in arms 1, 3, 4 and 9 in arm 2), 72% had T3–4 tumors, 85% had N2–3 nodal disease, and 67% had >10 pack-years of smoking. There were no DLTs in arms 1 and 2, 1 in arm 3 (mucositis), and 2 in arm 4 (lipase elevation and mucositis in 1 and fatigue in another). The most common grade ≥3 nivolumab-related adverse events were lipase increase, mucositis, diarrhea, lymphopenia, hyponatremia, leukopenia, fatigue, and serum amylase increase. Adjuvant nivolumab was feasible as defined in the protocol.

Conclusions: Concomitant nivolumab with the 4 tested regimens was safe for patients with intermediate- and high-risk HNSCC, and subsequent adjuvant nivolumab was feasible as defined (NCT02764593).

Introduction

Approximately 40% of patients with intermediate- or high-risk locoregionally advanced head and neck squamous cell carcinoma (HNSCC) experience disease progression within 5 years of standard-of-care every 3-week (q3 week) cisplatin and standard fractionated radiotherapy.[1,2] To date, neither accelerated fractionation nor the addition of the epidermal growth factor inhibitor cetuximab has improved survival outcomes.[1,3] HNSCC development is facilitated in part by immune evasion, including aberrant tumor expression of the programmed death ligand (PD-L) 1/PD-L2, resulting in suppression of tumor cell killing by tumor-infiltrating lymphocytes that express the programmed cell death protein-1 (PD-1) receptor.[4] Tumor PD-L1 expression is associated with reduced survival of patients with oral cavity squamous cell carcinoma, whereas high tumor-infiltrating lymphocytes are associated with improved survival of those with oropharyngeal cancers.[5] These data support the potential of inhibiting PD-1/PD-L1 checkpoint pathways to improve survival outcomes for this patient population.

PD-1/PD-L1 immune checkpoint blockade (ICB) with pembrolizumab or nivolumab has altered treatment paradigms for patients with recurrent or metastatic (R/M) HNSCC. In the first-line setting, the addition of pembrolizumab to platinum-doublet chemotherapy significantly improved overall survival.[6] In patients with platinumrefractory recurrent metastatic HNSCC, nivolumab significantly improved survival compared with single-agent therapy of investigators' choice.[7,8] Both pembrolizumab and nivolumab were approved for

the second-line treatment of R/M HNSCC in 2016. Given this therapeutic advancement in R/M HNSCC and evidence of PD-1 ICB synergistic activity with radiotherapy,[9–12] trials were rapidly designed to investigate whether the addition of a PD-1/PD-L1 ICB could improve survival of patients with newly diagnosed, locoregionally advanced (LRA) HNSCC.

We report here the results of a clinical trial designed to evaluate the safety, feasibility, and patient compliance with the addition of nivolumab to the 4 most frequently prescribed treatment regimens for primary therapy of newly diagnosed LRA HNSCC.

Methods and Materials

Protocol

Eligibility criteria for arms 1 to 4 included the following: untreated patients with pathologically confirmed American Joint Committee on Cancer 7th edition stage III to IV squamous cell carcinoma of the oral cavity, hypopharynx, larynx, or p16-negative oropharynx (T1-T2N2a-N3 or T3-4N0-N3)[13] or p16-positive oropharynx with smoking status >10 pack-years (T1-2N2b-N3 or T3-4N0-3) or ≤10 pack-years (T4N0-N3 or T1–3N3); Zubrod performance status 0 to 1 (arms 1–3)[14]; age ≥18 years; and adequate bone marrow, hepatic, and renal function (arms 1–3). Additional eligibility criteria for arm 4 only (eg, the platinum-ineligible group) included 1 or more of the following: age ≥70 years, Zubrod performance status 2, baseline grade ≥3 neuropathy, grade ≥2 hearing loss, or creatinine clearance <50 mL/min. Lifetime tobacco exposure was determined at enrollment by use of a standardized questionnaire.

Patients were enrolled sequentially in arms 1 to 3, and arm 4 was open concurrently with arms 1 to 3. Sequential enrollment to arms was chosen to facilitate a more rapid assessment of safety of each regimen than would be achieved with randomization. Intravenous systemic therapy differed by treatment arm, but the first dose of nivolumab was administered to all patients 14 days before the start of radiation therapy (RT). Patients assigned to arm 1 received nivolumab 240 mg every 14 days for 10 doses and cisplatin 40 mg/m^2 for 7 weekly doses concurrent with RT. Patients assigned to arm 2 received nivolumab 240 mg once, then nivolumab 360 mg every 21 days for 6 doses and cisplatin at a dose of 100 mg/m^2 on days 1, 22, and 43 of RT. Patients assigned to arm 3 received nivolumab 240 mg every 14 days for 10 doses and cetuximab 400 mg/m^2 loading 7 days before the start of RT followed by cetuximab 250 mg/m^2 for 7 weekly doses concurrent with RT. Patients in arm 4 received nivolumab 240 mg every 14 days for 10 doses and RT alone. All patients received maintenance nivolumab 480 mg every 28 days for 7 doses starting 12 weeks after completion of RT. All patients received standard fractionation intensity modulated RT (IMRT) that consisted of 70 Gy in 35 fractions (2 Gy/fraction) over 7 weeks to the primary tumor and involved nodes. The subclinical disease sites, which included a 10-mm margin around the primary tumor and elective nodal regions, received 56 Gy at 1.6 Gy/fraction using the simultaneous integrated boost technique. Regions that were considered high risk for microscopic disease such as the margin around endophytic tumors or the tumor/nodes with illdefined borders received 61.25 Gy at 1.75 Gy/fraction. Image guided RT was used for all patients, and all participating institutions were credentialed for head and neck IMRT and image guided RT before entering patients into the study.

Acute toxicity was evaluated weekly during RT and before each dose of nivolumab using Common Terminology Criteria for Adverse Events version 4 (http://ctep.info.nih.gov). The following additional laboratory tests were obtained to screen for potential nivolumab-related toxicities: alanine transaminase, aspartate transaminase, total bilirubin, alkaline phosphatase, amylase, lipase, and thyroid stimulating hormone at baseline, within 72 hours before each dose of nivolumab, during and up to 12 weeks after radiation treatment, then every 28 days during adjuvant nivolumab for all arms. In the event of toxicity, nivolumab administration was delayed, reinitiated, or discontinued per standard management algorithms (https://www.rtog.org/Clinical-Trials/Foundation-Studies/3504). Protocol-specified events of interest that are likely related to nivolumab include grade ≥2 drug-related uveitis; grade ≥3 drug-related pneumonitis, bronchospasm, diarrhea, colitis, neurologic adverse event (AE), hypersensitivity reaction, or infusion reaction; grade 3 drug-related thrombocytopenia >7 days or associated with bleeding that requires discontinuation; any grade 4 drug-related AE or laboratory abnormality associated with clinical sequelae or persisting despite appropriate corrective management or steroid; and any AE, laboratory abnormality, or intercurrent illness that, in the judgment of the investigator, presents a substantial clinical risk to the patient with continued nivolumab dosing. Criteria for dose delay, reduction, and discontinuation of weekly and q3 week cisplatin because of related toxicity were specified in the protocol. Calls were scheduled every other week among enrolling sites, the principal investigator, the committee chair, and the trial statistician to review AEs for dose-limiting toxicity (DLT) determination.

Physical examination and imaging studies were performed every 3 months for 2 years after completion of RT to assess late toxicities (Common Terminology Criteria for Adverse Events) and tumor status by Radiation Therapy Oncology Group (RTOG) criteria.[15,16] RTOG Foundation 3504 was registered with the National Cancer Institute (NCT02764593) and approved by the institutional review boards of all participating institutions. All patients provided written informed consent. Quality assurance reviews for administration of systemic therapy and RT were performed by RTOG Foundation standard operating procedures.

Laboratory studies

The analysis of tumor p16 status was restricted to patients with oropharyngeal squamous cell carcinoma.[17] Tumor p16 expression was evaluated by immunohistochemistry at the participating institution and confirmed by central review as positive using the H-score method as described by Jordan et al.[18] Sections from pretreatment formalin-fixed paraffin embedded tumor tissues were stained using the Agilent (formerly Dako) 28–8 IUO kit, containing monoclonal rabbit anti-PD-L1, primary antibody clone 28–8, by using the EnVision FLEX visualization system on a Dako Autostainer Link 48 system. A minimum of 100 cells were scored for each patient sample and was resulted as positive if more than 1% of the tumor cells exhibited partial or complete membranous expression of PD-L1. Negative reagent controls were evaluated in each case to confirm acceptable background staining. Staining intensity was not part of the evaluation. Tumor proportion score (TPS)[16,19] and combined positive score (CPS)[16,19] were generated for PD-L1 staining for each case.

RTOG Foundation 3504 was conducted by investigators at 9 institutions per contractual agreement with the RTOG Foundation and supported by Bristol-Myers Squibb. Study design and implementation, study data (collection, analysis, and interpretation), and manuscript preparation were performed by the authors as representatives of the RTOG Foundation and the RTOG Foundation Statistics and Data Management Center. The authors had complete access to all data. The first, second, and last authors serve as guarantors of all analyses and manuscript content.

Study design and statistical analysis

The principal objective of the study was to evaluate the safety of the addition of nivolumab to 4 standard-of-care chemoradiotherapy (CRT) regimens for the treatment of newly diagnosed LRA HNSCC. The primary endpoint was DLT and was defined as any grade ≥3 AE related to nivolumab that did not resolve to grade ≤1 within 28 days; a delay in RT of more than 2 weeks due to nivolumab-related toxicity; inability to complete RT due to nivolumab-related toxicity; or an inability to receive an adequate dose (≥70%) of cisplatin or cetuximab due to nivolumab-related toxicity. The period of DLT observation was from day −14 (start of nivolumab) to 28 days after completion of RT.

Ten patients were enrolled per arm to ensure a minimum of 8 evaluable patients for DLT, defined as those who received at least 1 dose of nivolumab, 1 fraction of RT, 1 dose of cisplatin or cetuximab (where applicable), and those who completed the DLT observation period (in the absence of DLT). Unevaluable patients were replaced, and the first 8 evaluable were analyzed for DLT. For each arm, the regimen would be considered safe if 0 to 2 patients experienced DLT events but too toxic if >2 of 8 patients had DLTs. With a cohort of 8 patients, the probability of the arm being judged to be too toxic when the true toxicity rate was 45% or higher was at least 78%. If the true toxicity rate was 20% or lower, the probability that the therapy would be too toxic was at most 20%.

The principal secondary objective included evaluation of the feasibility of 7 months of adjuvant nivolumab. Evidence of infeasibility included patient refusal, discontinuation due to DLT, and physician decision that therapy was no longer in the best interests of the patient in the absence of disease progression. If more than 4 of the first 8 evaluable patients across arms stopped the adjuvant therapy before 7 months, the adjuvant therapy was considered infeasible. The probability that adjuvant nivolumab was infeasible when the true noncompliance rate was 70% or higher was at least 81%. If the true noncompliance rate was 40% or lower, the probability that the therapy was feasible was 83%.

Disease progression and death counts were also reported. Progression was defined by Response Evaluation Criteria in Solid Tumors version 1.1 criteria or as clinical evidence of disease progression in a radiated field confirmed by cytology or histopathology. A positive biopsy at the primary site or involved nodes that occurred ≤20 weeks from the end of RT was categorized as disease persistence and >20 weeks as progression. Time to progression and death were measured from the date of treatment assignment and presented in swimmer plots. Median follow-up was calculated by the reverse Kaplan-Meier method and measured from date of treatment assignment. The association between CPS and TPS was measured by phi coefficient and compared by χ^2 test.

Results

From June 1, 2016, to September 27, 2018, 43 patients were enrolled at 9 institutions, and 40 eligible patients were assigned a treatment. A study schema is shown in Fig. 1. Because of cancer progression before initiation of therapy, 1 patient in arm 2 was excluded from analysis. The demographic and baseline characteristics of the 39 remaining patients are shown in Table 1. Median age was 62 years. A majority were male, White, and diagnosed with laryngeal or oropharyngeal cancer. Of the 39 patients, 61.5% had p16-positive oropharyngeal cancer, and median pack-years of tobacco smoking was 21 (range, 0–74).

AEs

Table E1 lists all grade 3 to 4 treatment-related AEs regardless of attribution. All patients in arms 1 to 3 experienced at least 1 grade 3 to 4 event related to protocol therapy, as did 7 of 10 patients in arm 4. AEs of grade ≥3 in 2 or more patients included gastrointestinal disorders (dysphagia, mucositis, nausea, vomiting, and diarrhea); investigations (lymphopenia, neutropenia, white blood cell decrease, lipase and amylase elevation, and weight loss); metabolism and nutrition disorders (anorexia, dehydration, and hyponatremia); ear and labyrinth disorders (hearing impairment); respiratory, thoracic, and mediastinal disorders (aspiration, dyspnea, and other); injury, poisoning, and procedural complications (dermatitis radiation); blood and lymphatic system disorders (anemia); and general disorders and administration site conditions (fatigue). Of note, there were no grade ≥3 renal and urinary disorders in either of the cisplatin arms and only 1 grade 3 radiation dermatitis each in the weekly cisplatin, cetuximab, and RT alone arms and none in the q3 week cisplatin arm. There was no grade 5 treatment-related death.

Shown in Table 2 are grade 3 to 4 AEs attributable to nivolumab. Grade ≥3 AEs were consistent with known toxicities of single-agent nivolumab and were more frequent in arms 1 and 4 than in arms 2 to 3. In all 39 patients, only 1 grade 4 nivolumab-attributable event of amylase increase was observed in arm 1.

A summary of DLTs is presented in Table 3. All of the DLTs were grade 3 nivolumab-attributable events that did not resolve within 28 days. Of the 10 patients enrolled in arm 1 (nivolumab plus weekly cisplatin), 2 withdrew consent during the DLT window and were considered unevaluable. None of the 8 evaluable patients experienced a DLT. Of the 9 evaluable patients in arm 2 (nivolumab plus q3 week cisplatin), none experienced a DLT. Of the 10 patients in arm 3 (nivolumab plus cetuximab), 1 withdrew consent during the DLT window and was considered unevaluable. One of the remaining 9 evaluable patients experienced a DLT, grade 3 mucositis. In arm 4, all 10 enrolled patients were evaluable. Three of 10 experienced 1 or more DLTs, including grade 3 lipase elevation and mucositis, fatigue, and lymphocyte count decrease. However, the regimen was considered safe per protocol because only 2 of the first 8 evaluable patients experienced a DLT. Therefore, all 4 regimens were considered safe and worthy of further investigation.

With regards to serious AEs (SAEs), there were 7 SAEs reported in 4 patients on arm 1 (Table E2). Arthralgia and myalgia were considered related to nivolumab. On arm 2,

there were 14 SAEs reported in 4 patients. Acute kidney injury and sinus tachycardia were considered related to nivolumab. The death not otherwise specify (cause of death unknown) occurred 234 days after completion of chemoradiation and 17 days after last nivolumab dose and was considered unrelated to chemoradiation or nivolumab. On arm 3, there were 13 SAEs reported in 5 patients. No SAEs on arm 3 were considered related to nivolumab. On arm 4, there were 15 SAEs reported in 5 patients. No SAEs on arm 4 were considered related to nivolumab. Grade 5 ventricular tachycardia occurred 14 days after completion of RT and 37 days after last nivolumab dose and was considered unrelated to radiation or nivolumab. The patient had a prior history of ventricular tachycardia. Grade 5 death due to head and neck cancer progression occurred 86 days after completion of RT and 37 days after last nivolumab dose and was considered unrelated to radiation or nivolumab.

Treatment compliance during RT portion

No treatment discontinuation of RT in arms 1 to 4 or of chemotherapy in arms 1 to 3 was attributable to nivolumab toxicity (Table 4). On arm 1, 8 of 10 patients received 70 Gy and 7 of 10 received ≥200 mg/m^2 cisplatin. Seven of 10 patients completed concurrent nivolumab. On arm 2, all 9 patients received 70 Gy and 8 of 9 received ≥200 mg/m^2 cisplatin. Seven of 9 patients completed concurrent nivolumab but 1 of the 7 completers refused adjuvant nivolumab. On arm 3, 7 of 10 patients received 70 Gy and 8 of 10 received 7 or 8 doses of cetuximab. Nine of 10 completed concurrent nivolumab but 1 of the 9 completers refused adjuvant nivolumab. On arm 4, all 10 patients received 70 Gy. Six of 10 patients completed concurrent nivolumab. See Table E3 for additional details of concurrent nivolumab.

Feasibility of adjuvant therapy

Of the first 8 evaluable patients across treatment arms, all 7 doses of adjuvant nivolumab were completed in 6 patients (Tables 4 and E4), so per the protocol design, the adjuvant nivolumab is considered feasible. Within each arm, 6 of 8, 3 of 8, 4 of 8, and 3 of 6 evaluable patients in arms 1, 2, 3, and 4, respectively, completed 7 doses of adjuvant nivolumab. Table E4 shows additional details of adjuvant nivolumab.

Follow-up

Patients were followed prospectively for 2 years after RT. At median follow-up of 2.2 years, 28 of 39 patients were alive without cancer progression. Time from treatment assignment to withdrawal of consent, cancer progression, death, or completion of 2 years of follow-up are provided in the form of swimmer plots in Fig. 2. We also stained tumor tissues for PD-L1 expression and determined that 17 (47%) of 36 evaluable tumor specimens were positive (ie, PD-L1 CPS ≥ 1). There was no obvious relationship between CPS/TPS and death or progression in this small group of patients (Fig. 2, Table E5). Note that there appears to be an association between CPS and TPS (Table E6).

Discussion

CRT is the current standard of care for patients with unresected locally advanced HNSCC; however, survival is not sufficiently high.[3] Immune checkpoint inhibitors have been approved for the treatment of patients with recurrent/metastatic HNSCC,[6,8] but there are

limited data for their use in the locoregionally advanced setting.[20] Addition of ICB to CRT for intermediate- or high-risk, locally advanced HNSCC might provide increased survival. In this population, there are currently several standards of care, including the 2 cisplatin-containing regimens based on the National Comprehensive Cancer Network guidelines.[21] Of note, during the time this trial was designed and enrolling patients (2016–2018), cetuximab was part of the standard of care because the results of RTOG 1016 were not released until late 2018, when most of the patients had been enrolled. Based on the findings of RTOG 1016,[22] cetuximab or RT alone is considered useful for those intolerant to systemic chemotherapy.[23]

The results from RTOG Foundation 3504 indicate that the addition of nivolumab to all 4 regimens evaluated was safe based upon the number of observed DLT events in each arm. The majority of patients completed RT per protocol. Three of 10 patients in the weekly cisplatin arm and 1 of 9 patients in the q3 week cisplatin arm received less than 200 mg/m^2 of concurrent cisplatin, a suggested important dose threshold.[24] Although these were due to patient refusal or toxicities not attributable to nivolumab, we cannot exclude the possibility that common toxicities attributable to chemotherapy were exacerbated by nivolumab, making the overall regimen intolerable to patients. The sequential, rather than randomized, assignment of patients to treatment arms could introduce selection bias and understate toxicities that would be experienced by an unselected patient population. Larger studies are needed to determine whether the addition of PD-1/L1 ICB could affect disease control by compromising systemic chemotherapy administration. A strategy to avoid compromising the concurrent chemoradiation treatment is to administer PD-1/L1 ICB after completion of RT as per the recently completed IMvoke 010 trial in HNSCC (NCT03452137) and the currently accruing Eastern Cooperative Oncology Group and the American College of Radiology Imaging Network 3161 trial in intermediate-risk human papillomavirus–related HNSCC (NCT03811015), analogous to the PACIFIC trial for patients with stage III non-small cell lung cancer.[25] A recently reported phase II randomized trial comparing concurrent or sequential fixed dose pembrolizumab with IMRT and weekly cisplatin suggested that sequential pembrolizumab yielded numerically higher 1- and 2-year progression-free survival compared with concurrent administration (NCT02777385).[26]

Across treatment arms in RTOG Foundation 3504, administration of adjuvant nivolumab for 1 year after RT was considered feasible per the protocol plan because the first 6 of 8 patients received all 7 cycles of nivolumab. These patients were primarily in arm 1 (weekly cisplatin arm); thus, the lack of randomization could have biased this endpoint. Because of this potential bias, we reported the number of patients who completed adjuvant nivolumab in each arm, although this was not part of the protocol analysis plan. As shown in Table 4, adjuvant nivolumab may only be feasible after radiation plus weekly cisplatin (arm 1) or radiation plus cetuximab (arm 3) but not after radiation plus every 3-week cisplatin (arm 2) or RT alone in cisplatin-ineligible patients (arm 4). Although the results from JAVELIN 100 suggested that adjuvant therapy with the PD-L1 inhibitor avelumab was feasible, a higher percentage of patients randomized to the avelumab arm (149 of 291, 51%) discontinued the adjuvant treatment early compared with the placebo arm (110 of 304, 39%).[20] If the primary benefit of immune checkpoint inhibitors is in the adjuvant phase, methods to improve patient compliance require further investigation.

The JAVELIN Head and Neck 100 trial of avelumab plus chemoradiotherapy is the first report of a randomized, phase 3 study of an immune checkpoint inhibitor combined with chemoradiotherapy and the first report of a phase 3 trial investigating an immune checkpoint inhibitor in LRA HNSCC.[20] Avelumab plus chemoradiotherapy followed by avelumab maintenance did not significantly improve progression-free survival compared with placebo plus chemoradiotherapy followed by placebo maintenance. Based on an exploratory analysis, a potential progression-free survival benefit was observed with avelumab plus chemoradiation in patients whose tumors expressed high levels of PD-L1, and this could be explored further in future studies. These findings will help inform the design of ongoing and future trials and highlight the need for more research into the effects of the combination of ICB plus chemoradiotherapy in LRA HNSCC. Unfortunately, although not yet available for peer review, the addition of concurrent and maintenance pembrolizumab to chemoradiotherapy did not significantly improve event-free survival in Keynote 412 (NCT03040999).[27] A recent preclinical study showed that blockade of the PD-1 pathway after local tumor irradiation resulted in the expansion of polyfunctional intratumoral $CD8^+$ T cells, a decrease in intratumoral dysfunctional $CD8^+$ T cells, expansion of reprogrammable $CD8^+$ T cells, and induction of potent abscopal responses, whereas administration of aPD-1 before irradiation almost completely abrogated systemic immunity due to the death of $CD8^+$ T cells and subsequent reduction of polyfunctional effector $CD8^+$ T cells at the irradiated tumor site.[28] Whether this observation is clinically relevant is being studied in ongoing trials.

Unlike the JAVELIN 100 trial, we did not observe a relationship between CPS or TPS score with treatment outcome in our patients. However, the number of patients was too small, and the number of events in arms 1 and 2 was too few in our study to rigorously assess association. The results of the highly anticipated IMvoke 010 trial (NCT03452137) and EA3161 in HNSCC will help determine whether the addition of adjuvant PD1/PDL1 ICB to CRT will benefit patients with LRA HNSCC and which patient subsets, if any, would be best served with this approach.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Disclosures:

This project was supported by Bristol Myers Squibb (BMS).

A.D.C. declares during the past 36 months NRG funded the trial and BMS funded NRG. W.J.C. declares during the past 36 months chair of BMS Data Monitoring Committee (DMC). J.F.D. declares during the past 36 months payments made to institution for study-related and patient-care costs (NRG Foundation) and payments to institution for study-related and patient- care costs (Merck, Bayer, Beigene, NRG). Nonpaid FDA Oncology Drug Advisory Committee and ASCO Government Relations Committee (during time of study, 3-year term). R.L.F. declares during the past 36 months payments made to institution for grants of contracts (Astra-Zeneca/MedImmune, Bristol-Myers Squibb, Merck, Novasenta, Tesaro), payments made for consulting (Adagene Inc, Aduro Biotech, Inc, Bicara Therapeutics, Inc, Brooklyn Immunotherapeutics, LLC, Catenion, Everest Clinical Research Corporation, F. Hoffman-La Roche Ltd, Genocea Biosciences, Inc, Kowa

Research Institute, Inc, Mirati Therapeutics, Inc, Nanobiotix, Novasenta, PPD Development, LP, Sanofi, Zymerworks, Inc), participation on a data safety monitoring board or advisory board (Bristol-Myers Squibb, Coherus BioSciences, Inc, Hookipa Biotech GmbH, Instil Bio, Inc, Lifescience Dynamics Limited, MacroGenics, Inc, Merck, Mirror Biologics Inc, Numab Therapeutics GA, OncoCyte Corp, Pfizer, Rakuten Medical, Inc, Seagen, Inc, SIRPant Immunotherapeutics, Inc, Vir Biotechnology, Inc), stock or stock options (Novasenta). M.F.G. declares during the past 36 months grants or contracts (Varian Medical Systems, RefleXion Medical) and stock or stock options (Roche). M.L.G. all support for the present manuscript (NIDCR), declares during the past 36 months grants or contracts (NIDCR), consulting fees (Istari Oncology Inc, LLX Solutions, LLC, Kura Oncology, Mirati, Therapeutics, BioNtech, AG, Bristol-Myers Squibb, Bicara Therapeutics, Bayer Healthcare Pharmaceutics, Genocea Biosciences, Inc, Shattuck Labs, Inc, EMD Serono, Inc, Debiopharm, Merck & Co, Ipsen Biopharmaceuticals, Inc, Gilead Sciences, Inc, Coherus), payment or honoraria (OncLive, Roche), support for attending meetings and/or travel (AACR), patents planned, issued, or pending (sponsor-investigator for pNGVL4a- Sig/E7 [detox]/HSP70 plasmid DNA for a clinical protocol entitled “An open-label phase one study of the safety with stage III or IV HPV16-positive head and neck squamous cell carcinoma” [issued]; “Oral HPV infection detection for oral cancer screening and diagnosis” [pending]; “HPV mRNA detection on oral cytology specimens for diagnosis and screening for oral cancer [pending]), participation on a data safety monitoring board or advisory board (Seagen, Sensei Biotherapeutics, Inc, SQZBiotech, BioMimetix, Kura), stock options (Sensei), other financial or nonfinancial interests: research funding (Genocea Biosciences, Inc, Bristol-Myers Squibb, Genentech, Kura, Cullinan Labs, Agenus). R.J.K. declares during the past 36 months grants or contracts (NIH grants R37 CA255330, P30 CA014520, P50 CA174509, UG3 DE030431), consulting fees (Systematic Management Services, Inc, MELE Associates, Inc), multiple leadership roles (ASTRO). L.K.M. declares during the past 36 months grants or contracts (Merck, Astra-Zeneca), participation on a data safety monitoring board or advisory board (Cel-Sci). M.M. declares during the past 36 months grants or contracts (Astra Zeneca, ViewRay, Elekta, Varian), consulting fees and payment or honoraria (Astra Zeneca), support for attending meetings and/or travel (ViewRay, Elekta, Varian). R.S.L. declares during the past 36 months grants or contracts (BMS, Clinigen, Celldex), support for attending meetings and/or travel (BMS), participation on a data safety monitoring board or advisory board (Incyte, BMS). Q.T.L. declares during the past 36 months support for paid flights and hotel (RTOG Foundation) retreat meetings, leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid (RTOG Group Chair [NRG Oncology]). P.T.-S. declares NRG Oncology SDMC grant (NCI). M.-T.T.: Honoraria (National Cancer Institute PDQ, University of Maryland Visiting Professor Lecture). N.F.S. declares during the past 36 months royalties (Springer), consulting fees (Pfizer, GSK, Aduro, Merck, BioNTech, Reach MD, WebMD, Kura, CUE), payment or honoraria (Springer), participation on a data safety monitoring board or advisory board (Pfizer). A.C. declares during the past 36 months grants or contracts (UG1 CA233331 [MPI: Verschraegen/Carson/Chakravarti/O’Malley/Carbone], 03/28/2019–02/28/2025 [NCI], K12CA133250 [NCI; PI: Byrd], 06/01/2014–06/30/2024, 1R01CA227874–03 [PI: Guo, Chakravarti], 06/02/2019–07/01/2024 1R01CA1145 128–06 [PI: Chakravarti], 04/01/2015 06/30/2022 Thrasher-82100815 [PI: Chakravarti], 08/01/2016–07/31/2020 R01NS104332 [PI: Guo, Chakravarti], 09/15/2018 to 06/30/2023, R01CA227874 [PI: Guo, Chakravarti], 7/01/2019 to 06/30/2024 [NCI], R01CA188228–06 [PI: Beroukhim, Chakravarti, Ligon], Varian grant [PI: Chakravarti], 12/07/2018–12/30/2021, Varian/OSU Linac Gift in Kind Grant [PI: Chakravarti] 6/15/2021–6/15/2024).

A.D.C. declares during the past 36 months NRG funded the trial and BMS funded NRG. W.J.C. declares during the past 36 months chair of BMS Data Monitoring Committee (DMC). J.F.D. declares during the past 36 months payments made to institution for study-related and patient-care costs (NRG Foundation) and payments to institution for study-related and patient- care costs (Merck, Bayer, Beigene, NRG). Nonpaid FDA Oncology Drug Advisory Committee and ASCO Government Relations Committee (during time of study, 3-year term). R.L.F. declares during the past 36 months payments made to institution for grants of contracts (Astra-Zeneca/MedImmune, Bristol-Myers Squibb, Merck, Novasenta, Tesaro), payments made for consulting (Adagene Inc, Aduro Biotech, Inc, Bicara Therapeutics, Inc, Brooklyn Immunotherapeutics, LLC, Catenion, Everest Clinical Research Corporation, F. Hoffman-La Roche Ltd, Genocea Biosciences, Inc, Kowa Research Institute, Inc, Mirati Therapeutics, Inc, Nanobiotix, Novasenta, PPD Development, LP, Sanofi, Zymerworks, Inc), participation on a data safety monitoring board or advisory board (Bristol-Myers Squibb, Coherus BioSciences, Inc, Hookipa Biotech GmbH, Instil Bio, Inc, Lifescience Dynamics Limited, MacroGenics, Inc, Merck, Mirror Biologics Inc, Numab Therapeutics GA, OncoCyte Corp, Pfizer, Rakuten Medical, Inc, Seagen, Inc, SIRPant Immunotherapeutics, Inc,

Vir Biotechnology, Inc), stock or stock options (Novasenta). M.F.G. declares during the past 36 months grants or contracts (Varian Medical Systems, RefleXion Medical) and stock or stock options (Roche). M.L.G. all support for the present manuscript (NIDCR), declares during the past 36 months grants or contracts (NIDCR), consulting fees (Istari Oncology Inc, LLX Solutions, LLC, Kura Oncology, Mirati, Therapeutics, BioNtech, AG, Bristol-Myers Squibb, Bicara Therapeutics, Bayer Healthcare Pharmaceutics, Genocea Biosciences, Inc, Shattuck Labs, Inc, EMD Serono, Inc, Debiopharm, Merck & Co, Ipsen Biopharmaceuticals, Inc, Gilead Sciences, Inc, Coherus), payment or honoraria (OncLive, Roche), support for attending meetings and/or travel (AACR), patents planned, issued, or pending (sponsor-investigator for pNGVL4a- Sig/E7 [detox]/HSP70 plasmid DNA for a clinical protocol entitled “An open-label phase one study of the safety with stage III or IV HPV16-positive head and neck squamous cell carcinoma” [issued]; “Oral HPV infection detection for oral cancer screening and diagnosis” [pending]; “HPV mRNA detection on oral cytology specimens for diagnosis and screening for oral cancer [pending]), participation on a data safety monitoring board or advisory board (Seagen, Sensei Biotherapeutics, Inc, SQZBiotech, BioMimetix, Kura), stock options (Sensei), other financial or nonfinancial interests: research funding (Genocea Biosciences, Inc, Bristol-Myers Squibb, Genentech, Kura, Cullinan Labs, Agenus). R.J.K. declares during the past 36 months grants or contracts (NIH grants R37 CA255330, P30 CA014520, P50 CA174509, UG3 DE030431), consulting fees (Systematic Management Services, Inc, MELE Associates, Inc), multiple leadership roles (ASTRO). L.K.M. declares during the past 36 months grants or contracts (Merck, Astra-Zeneca), participation on a data safety monitoring board or advisory board (Cel-Sci). M.M. declares during the past 36 months grants or contracts (Astra Zeneca, ViewRay, Elekta, Varian), consulting fees and payment or honoraria (Astra Zeneca), support for attending meetings and/or travel (ViewRay, Elekta, Varian). R.S.L. declares during the past 36 months grants or contracts (BMS, Clinigen, Celldex), support for attending meetings and/or travel (BMS), participation on a data safety monitoring board or advisory board (Incyte, BMS). Q.T.L. declares during the past 36 months support for paid flights and hotel (RTOG Foundation) retreat meetings, leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid (RTOG Group Chair [NRG Oncology]). P.T.-S. declares NRG Oncology SDMC grant (NCI). M.-T.T.: Honoraria (National Cancer Institute PDQ, University of Maryland Visiting Professor Lecture). N.F.S. declares during the past 36 months royalties (Springer), consulting fees (Pfizer, GSK, Aduro, Merck, BioNTech, Reach MD, WebMD, Kura, CUE), payment or honoraria (Springer), participation on a data safety monitoring board or advisory board (Pfizer). A.C. declares during the past 36 months grants or contracts (UG1 CA233331 [MPI: Verschraegen/Carson/Chakravarti/O’Malley/Carbone], 03/28/2019–02/28/2025 [NCI], K12CA133250 [NCI; PI: Byrd], 06/01/2014–06/30/2024, 1R01CA227874–03 [PI: Guo, Chakravarti], 06/02/2019–07/01/2024 1R01CA1145 128–06 [PI: Chakravarti], 04/01/2015 06/30/2022 Thrasher-82100815 [PI: Chakravarti], 08/01/2016–07/31/2020 R01NS104332 [PI: Guo, Chakravarti], 09/15/2018 to 06/30/2023, R01CA227874 [PI: Guo, Chakravarti], 7/01/2019 to 06/30/2024 [NCI], R01CA188228–06 [PI: Beroukhim, Chakravarti, Ligon], Varian grant [PI: Chakravarti], 12/07/2018–12/30/2021, Varian/OSU Linac Gift in Kind Grant [PI: Chakravarti] 6/15/2021–6/15/2024).

Data sharing statement:

Please submit requests for data sharing to RTOG-Publications@acr.org.

References

1. Ang KK, Harris J, Wheeler R, et al. Human papillomavirus and survival of patients with oropharyngeal cancer. N Engl J Med 2010;363:24–35. [PubMed: 20530316]
2. Bigelow EO, Harris J, Fakhry C, et al. Risk stratification after recurrence of human papillomavirus (HPV)-related and non-HPV-related oropharyngeal cancer: Secondary analysis of NRG oncology RTOG 0129 and 0522. Head Neck 2022;44:158–167. [PubMed: 34729846]
3. Ang KK, Zhang Q, Rosenthal DI, et al. Randomized phase III trial of concurrent accelerated radiation plus cisplatin with or without cetuximab for stage III to IV head and neck carcinoma: RTOG 0522. J Clin Oncol 2014;32:2940–2950. [PubMed: 25154822]
4. Kansy BA, Concha-Benavente F, Srivastava RM, et al. PD-1 status in CD8(+) T cells associates with survival and anti-PD-1 therapeutic outcomes in head and neck cancer. Cancer Res 2017;77:6353–6364. [PubMed: 28904066]
5. Hartman DJ, Ahmad F, Ferris RL, Rimm DL, Pantanowitz L. Utility of CD8 score by automated quantitative image analysis in head and neck squamous cell carcinoma. Oral Oncol 2018;86:278–287. [PubMed: 30409313]
6. 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;394:1915–1928. [PubMed: 31679945]

7. 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;375:1856–1867. [PubMed: 27718784]
8. Ferris RL, Blumenschein G Jr., Fayette J, et al. Nivolumab vs investigator's choice in recurrent or metastatic squamous cell carcinoma of the head and neck: 2-year long-term survival update of CheckMate 141 with analyses by tumor PD-L1 expression. Oral Oncol 2018;81:45–51. [PubMed: 29884413]
9. Ko EC, Formenti SC. Radiotherapy and checkpoint inhibitors: A winning new combination? Ther Adv Med Oncol 2018;10: 1758835918768240. [PubMed: 29662550]
10. Stransky B, de Souza SJ. Modeling tumor evolutionary dynamics. Front Physiol 2012;3:480. [PubMed: 23420281]
11. Yi M, Qin S, Zhao W, Yu S, Chu Q, Wu K. The role of neoantigen in immune checkpoint blockade therapy. Exp Hematol Oncol 2018;7:28. [PubMed: 30473928]
12. Wijetunga NA, Yu Y, Morris LG, Lee N, Riaz N. The head and neck cancer genome in the era of immunotherapy. Oral Oncol 2021;112: 105040. [PubMed: 33197752]
13. Flaming I, Cooper J, Henson D, et al. AJCC Cancer Staging Manual. 5th ed. Philadephia: Lippincott-Raven; 1997.
14. Oken M, Creech R, Torney D, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982;5:649–655. [PubMed: 7165009]
15. Cox J, Stetz J, Pajak T. Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organisation for Research and Treatment of Cancer (EORTC). Int J Radiat Oncol Biol Phys 1995;31:1341–1346. [PubMed: 7713792]
16. Hirsch FR, McElhinny A, Stanforth D, et al. PD-L1 Immunohistochemistry assays for lung cancer: Results from phase 1 of the blueprint PD-L1 IHC assay comparison project. J Thorac Oncol 2017;12:208–222. [PubMed: 27913228]
17. Gillison M, D'souza G, Westra W, et al. Distinct risk factor profiles for human papillomaviurs type 16-positive and human papillomavirus 16-negative head and neck cancers. J Natl Cancer Inst 2008;100:407–420. [PubMed: 18334711]
18. Jordan RC, Lingen MW, Perez-Ordonez B, et al. Validation of methods for oropharyngeal cancer HPV status determination in US cooperative group trials. Am J Surg Pathol 2012;36:945–954. [PubMed: 22743284]
19. Paver EC, Cooper WA, Colebatch AJ, et al. Programmed death ligand-1 (PD-L1) as a predictive marker for immunotherapy in solid tumours: A guide to immunohistochemistry implementation and interpretation. Pathology 2021;53:141–156. [PubMed: 33388161]
20. 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;22:450–462. [PubMed: 33794205]
21. Caudell JJ, Gillison ML, Maghami E, et al. NCCN guidelines(R) insights: Head and neck cancers, version 1.2022. J Natl Compr Canc Netw 2022;20:224–234. [PubMed: 35276673]
22. Gillison ML, Trotti AM, Harris J, et al. Radiotherapy plus cetuximab or cisplatin in human papillomavirus-positive oropharyngeal cancer (NRG Oncology RTOG 1016): A randomised, multicentre, non-inferiority trial. Lancet 2019;393:40–50. [PubMed: 30449625]
23. Ogden GR. Complete resorption of the mandibular condyles in rheumatoid arthritis. Br Dent J 1986;160:95–97. [PubMed: 3456239]
24. Nwizu T, Adelstein DJ. In squamous cell head and neck cancer: Which platinum, how much and how often? Expert Rev Anticancer Ther 2014;14:1033–1039. [PubMed: 24998393]
25. Antonia SJ, Villegas A, Daniel D, et al. Durvalumab after chemoradiotherapy in stage III non-small-cell lung cancer. N Engl J Med 2017;377:1919–1929. [PubMed: 28885881]
26. Clump DA, Zandberg DP, Skinner HD, et al. A randomized phase II study evaluating concurrent or sequential fixed-dose immune therapy in combination with cisplatin and intensity-modulated radiotherapy in intermediate- or high-risk, previously untreated, locally advanced head and neck cancer (LA SCCHN). ASCO Annual Meeting, June 3-7, Chicago, IL; 2022.
27. Merck. Merck provides update on phase 3 KEYNOTE-412 trial in unresected locally advanced head and neck squamous cell carcinoma.

Available at: https://www.merck.com/news/merck-provides-update-on-phase-3-keynote-412-trial-in-unresected-locally-advanced-head-and-neck-squamous-cell-carcinoma/. Accessed September 6, 2022.

28. Wei J, Montalvo-Ortiz W, Yu L, et al. Sequence of alphaPD-1 relative to local tumor irradiation determines the induction of abscopal antitumor immune responses. Sci Immunol 2021;6: eabg0117. [PubMed: 33837124]

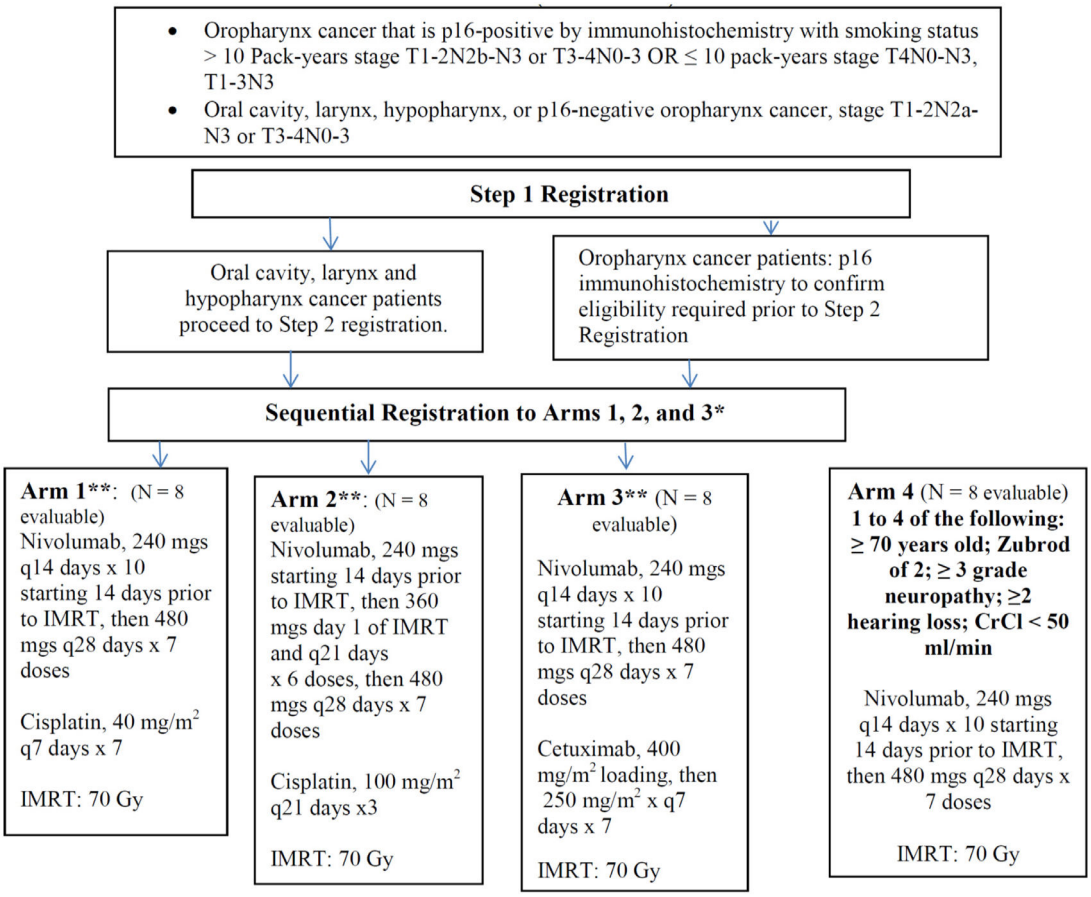
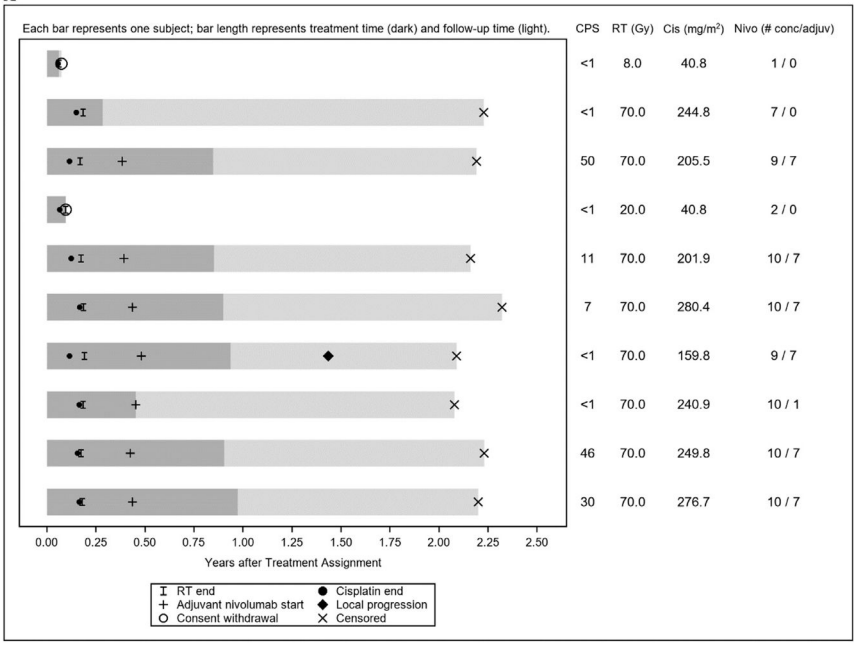
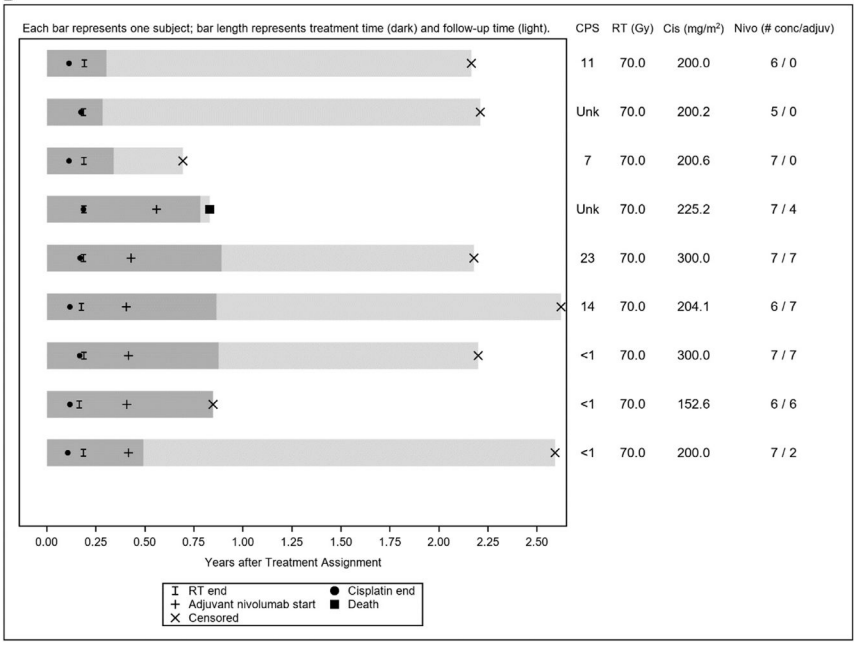


Fig. 1.
Study schema for RTOG Foundation 3504.

A



B



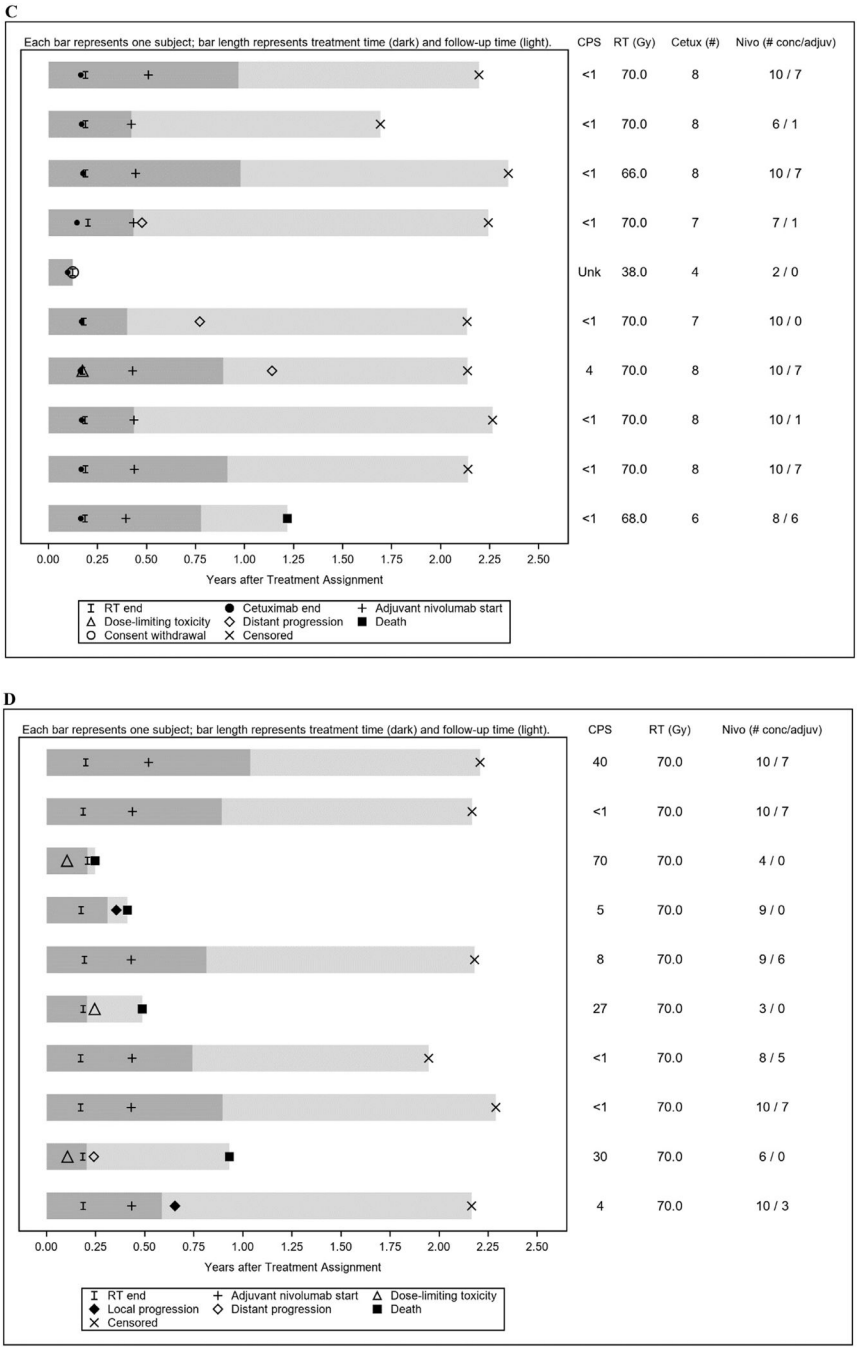


Fig. 2.

Years from treatment assignment to end of treatment, consent withdrawal, disease progression, and death in arm 1 (A), arm 2 (B), arm 3 (C), and arm 4 (D).

Table 1

Patient and tumor characteristics

	Arm 1: RT + cisq7 + nivo (n = 10)	Arm 2: RT + cis q21 + nivo (n = 9)	Arm 3: RT + cetux + nivo (n = 10)	Arm 4: RT + nivo (n = 10)	Total (N = 39)
Age (y)					
Median	56	55	61.5	74.5	62
Minimum to maximum	48–66	35–76	50–81	61–84	35–84
Q1–Q3	53–62	46–65	60–68	69–78	55–70
<40	0 (0.0%)	2 (22.2%)	0 (0.0%)	0 (0.0%)	2 (5.1%)
40–49	1 (10.0%)	1 (11.1%)	0 (0.0%)	0 (0.0%)	2 (5.1%)
50–59	5 (50.0%)	2 (22.2%)	1 (10.0%)	0 (0.0%)	8 (20.5%)
60–69	4 (40.0%)	3 (33.3%)	7 (70.0%)	3 (30.0%)	17 (43.6%)
≥70	0 (0.0%)	1 (11.1%)	2 (20.0%)	7 (70.0%)	10 (25.6%)
Sex					
Male	8 (80.0%)	6 (66.7%)	8 (80.0%)	9 (90.0%)	31 (79.5%)
Female	2 (20.0%)	3 (33.3%)	2 (20.0%)	1 (10.0%)	8 (20.5%)
Race					
Black or African American	1 (10.0%)	2 (22.2%)	0 (0.0%)	1 (10.0%)	4 (10.3%)
White	9 (90.0%)	7 (77.8%)	7 (70.0%)	9 (90.0%)	32 (82.1%)
Unknown or not reported	0 (0.0%)	0 (0.0%)	3 (30.0%)	0 (0.0%)	3 (7.7%)
Ethnicity					
Hispanic or Latino	1 (10.0%)	0 (0.0%)	1 (10.0%)	0 (0.0%)	2 (5.1%)
Not Hispanic or Latino	9 (90.0%)	9 (100.0%)	9 (90.0%)	10 (100.0%)	37 (94.9%)
Zubrod performance status					
0	4 (40.0%)	3 (33.3%)	7 (70.0%)	5 (50.0%)	19 (48.7%)
1	6 (60.0%)	6 (66.7%)	3 (30.0%)	4 (40.0%)	19 (48.7%)
2	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (10.0%)	1 (2.6%)
Smoking history (pack-years)					
Median	28.5	0	15	37.5	21
Minimum to maximum	0–40	0–42	0–53	0–74	0–74
Q1–Q3	20–32	0–6	12–25	22–51	0–34
≤10	2 (20.0%)	7 (77.8%)	2 (20.0%)	2 (20.0%)	13 (33.3%)

Int J Radiat Oncol Biol Phys. Author manuscript; available in PMC 2024 June 20.

	Arm 1: RT + cisq7 + nivo (n = 10)	Arm 2: RT + cis q21 + nivo (n = 9)	Arm 3: RT + cetux + nivo (n = 10)	Arm 4: RT + nivo (n = 10)	Total (N = 39)
>10	8 (80.0%)	2 (22.2%)	8 (80.0%)	8 (80.0%)	26 (66.7%)
Primary site					
Larynx	5 (50.0%)	2 (22.2%)	0 (0.0%)	3 (30.0%)	10 (25.6%)
Hypopharynx	0 (0.0%)	0 (0.0%)	2 (20.0%)	0 (0.0%)	2 (5.1%)
Oropharynx p16-negative	0 (0.0%)	0 (0.0%)	2 (20.0%)	1 (10.0%)	3 (7.7%)
Oropharynx p16-positive	5 (50.0%)	7 (77.8%)	6 (60.0%)	6 (60.0%)	24 (61.5%)
T stage (clinical)					
T1	0 (0.0%)	1 (11.1%)	2 (20.0%)	1 (10.0%)	4 (10.3%)
T2	2 (20.0%)	1 (11.1%)	2 (20.0%)	2 (20.0%)	7 (17.9%)
T3	5 (50.0%)	2 (22.2%)	0 (0.0%)	2 (20.0%)	9 (23.1%)
T4	3 (30.0%)	5 (55.6%)	6 (60.0%)	5 (50.0%)	19 (48.7%)
N stage (clinical)					
N0	1 (10.0%)	1 (11.1%)	0 (0.0%)	1 (10.0%)	3 (7.7%)
N1	1 (10.0%)	0 (0.0%)	0 (0.0%)	2 (20.0%)	3 (7.7%)
N2a	0 (0.0%)	0 (0.0%)	1 (10.0%)	0 (0.0%)	1 (2.6%)
N2b	4 (40.0%)	3 (33.3%)	3 (30.0%)	2 (20.0%)	12 (30.8%)
N2c	4 (40.0%)	3 (33.3%)	5 (50.0%)	4 (40.0%)	16 (41.0%)
N3	0 (0.0%)	2 (22.2%)	1 (10.0%)	1 (10.0%)	4 (10.3%)
PD-L1 TPS	(n = 10)	(n = 8)	(n = 10)	(n = 10)	(n = 38)
0	6 (60.0%)	6 (75.0%)	8 (80.0%)	3 (30.0%)	23 (60.5%)
1+	4 (40.0%)	2 (25.0%)	2 (20.0%)	7 (70.0%)	15 (39.5%)
PD-L1 CPS	(n = 10)	(n = 7)	(n = 9)	(n = 10)	(n = 36)
<1	5 (50.0%)	3 (42.9%)	8 (88.9%)	3 (30.0%)	19 (52.8%)
1+	5 (50.0%)	4 (57.1%)	1 (11.1%)	7 (70.0%)	17 (47.2%)

Data are presented as n (%) unless otherwise indicated.

Abbreviations: cetux = cetuximab; cis = cisplatin; CPS = combined positive score; nivo = nivolumab; PD-L1 = programmed death ligand; Q1 = first quartile; Q3 = third quartile; q7 = every 7 days or weekly; q21 = every 21 days or every 3 weeks; RT = radiation therapy; TPS = tumor proportion score.

Int J Radiat Oncol Biol Phys. Author manuscript; available in PMC 2024 June 20.

Table 2

Grade 3–4 nivo-related adverse events

System organ class/term	Arm 1: RT + cisq7 + nivo (n = 10) n (%) of patients by grade		Arm 2 RT + cisq21 + nivo (n = 9) n (%) of patients by grade		Arm 3: RT + cetux + nivo (n = 10) n (%) of patients by grade		Arm 4: RT + nivo (n = 10) n (%) of patients by grade	
	3	4	3	4	3	4	3	4
Overall highest grade	7	1	4	0	4	0	7	0
	(70.0)	(10.0)	(44.4)	(0.0)	(40.0)	(0.0)	(70.0)	(0.0)
Anemia	0	0	0	0	0	0	1	0
	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(10.0)	(0.0)
Adrenal insufficiency	1	0	0	0	0	0	0	0
	(10.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)
Diarrhea	1	0	2	0	0	0	0	0
	(10.0)	(0.0)	(22.2)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)
Mucositis oral	1	0	0	0	1	0	2	0
	(10.0)	(0.0)	(0.0)	(0.0)	(10.0)	(0.0)	(20.0)	(0.0)
Fatigue	1	0	0	0	0	0	1	0
	(10.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(10.0)	(0.0)
Lipase increased	2	0	2	0	1	0	1	0
	(20.0)	(0.0)	(22.2)	(0.0)	(10.0)	(0.0)	(10.0)	(0.0)
Lymphocyte count decreased	1	0	0	0	0	0	2	0
	(10.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(20.0)	(0.0)
Neutrophil count decreased	1	0	0	0	0	0	0	0
	(10.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)
Serum amylase increased	0	1	1	0	0	0	0	0
	(0.0)	(10.0)	(11.1)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)
White blood cell decreased	2	0	0	0	0	0	0	0
	(20.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)
Anorexia	1	0	0	0	0	0	0	0
	(10.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)
Hyponatremia	0	0	0	0	2	0	1	0
	(0.0)	(0.0)	(0.0)	(0.0)	(20.0)	(0.0)	(10.0)	(0.0)

Int J Radiat Oncol Biol Phys. Author manuscript; available in PMC 2024 June 20.

System organ class/term	Arm 1: RT + cisq7 + nivo (n = 10) n (%) of patients by grade		Arm 2 RT + cisq21 + nivo (n = 9) n (%) of patients by grade		Arm 3: RT + cetux + nivo (n = 10) n (%) of patients by grade		Arm 4: RT + nivo (n = 10) n (%) of patients by grade	
	3	4	3	4	3	4	3	4
Rash maculo-papular	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (10.0)	0 (0.0)

Adverse events were graded with CTCAE version 4.

Abbreviations: cetux = cetuximab; cis = cisplatin; CTCAE = Common Terminology Criteria for Adverse Events; nivo = nivolumab; q7 = every 7 days or weekly; q21 = every 21 days or every 3 weeks; RT = radiation therapy.

Int J Radiat Oncol Biol Phys. Author manuscript; available in PMC 2024 June 20.

Table 3

DLT summary

	Arm 1:RT + cisq7 + nivo	Arm 2:RT + cisq21 + nivo	Arm 3:RT + cetux + nivo	Arm 4:RT + nivo
DLTs in first 8 evaluable patients	0/8	0/8	1/8	2/8
DLTs in all evaluable patients	0/8	0/9	1/9	3/10

Two patients in arm 1 and 1 in arm 3 were unevaluable because of consent withdrawal during the DLT observation period. The DLT in arm 3 was grade 3 oral mucositis with duration 38 days. The DLTs in the first 8 evaluable patients in arm 4 were (1) grade 3 lipase increased with duration 52 days and grade 3 oral mucositis with duration 42 days and (2) grade 3 fatigue with duration 89 days. The third DLT in arm 4 was grade 3 lymphocyte count decreased with duration 49 days.

Abbreviations: cetux = cetuximab; cis = cisplatin; DLT = dose-limiting toxicity; nivo = nivolumab; q7 = every 7 days or weekly; q21 = every 21 days or every 3 weeks; RT = radiation therapy.

Int J Radiat Oncol Biol Phys. Author manuscript; available in PMC 2024 June 20.

Table 4

Treatment delivery

RT		Cis/cetux			Nivo	
Reason ended	**Total dose (Gy)**	**Reason ended**	**Number of doses**	**Total dose (mg/m^2)**	**Reason ended**	**Number of doses (concurrent/adjuvant)**
Arm 1: RT + cis q7 + nivo (n = 10)						
Completed	70.00	Completed	7	280.38	Completed	10/7
Completed	70.00	Completed	7	276.68	Completed	10/7
Completed	70.00	Completed	7	249.81	Completed	10/7
Completed	70.00	Completed	6	240.87	AE (grade 3 adrenal insufficiency related to nivo)	10/1
Completed	70.00	AE (grade 1 creatinine increased unrelated to nivo)	6	244.84	AE (grade 2 blurred vision related to nivo)	7/0
Completed	70.00	AE (grade 4 neutrophil count decreased unrelated to nivo)	5	205.49	Completed	9/7
Completed	70.00	AE (grade 3 neutrophil count decreased unrelated to nivo)	5	201.94	Completed	10/7
Completed	70.00	AE (grade 3 anaphylaxis unrelated to nivo)	4	159.83	Completed	9/7
Patient refusal	20.00	Patient refusal	1	40.83	Patient refusal	2/0
Patient refusal	8.00	Patient refusal	1	40.80	AE (grade 4 serum amylase increased related to nivo)	1/0
Arm 2: RT + cis q21 + nivo (n = 9)						
Completed	70.00	Completed	3	300.00	Completed	7/7
Completed	70.00	Completed	3	300.00	Completed	7/7
Completed	70.00	Completed	3	225.16	Death (NOS, unrelated to treatment)	7/4
Completed	70.00	Completed	3	200.23	AE (grade 2 fatigue related to nivo)	5/0
Completed	70.00	AE (grade 3 nausea; grade 2 vomiting; grade 2 sinusitis; grade 2 neutrophil count decreased; all unrelated to nivo)	2	204.15	Completed	6/7
Completed	70.00	AE (grade 3 neutrophil count decreased unrelated to nivo)	2	200.60	Patient refusal	7/0
Completed	70.00	AE (grade 3 febrile neutropenia; grade 3 lung infection; both unrelated to nivo)	2	200.00	AE (grade 3 diarrhea related to nivo)	7/2

RT		Cis/cetux			Nivo	
Reason ended	**Total dose (Gy)**	**Reason ended**	**Number of doses**	**Total dose (mg/m^2)**	**Reason ended**	**Number of doses (concurrent/adjuvant)**
Completed	70.00	AE (grade 3 neutrophil count decreased unrelated to nivo)	2	200.00	AE (grade 2 arthralgia related to nivo)	6/0
Completed	70.00	Other (cis dose 2 was deferred, patient had completed radiation before when third dose of cis would have been due)	2	152.59	Patient refusal	6/6
Arm 3: RT + cetux + nivo (n = 10)						
Completed	70.00	Completed	8	2222.08	Patient refusal	10/1
Completed	70.00	Completed	8	2215.45	Completed	10/7
Completed	70.00	Completed	8	2211.82	AE (grade 2 diarrhea related to nivo)	6/1
Completed	70.00	Completed	8	2184.72	Completed	10/7
Completed	70.00	Completed	8	2151.79	Completed	10/7
Completed	70.00	Completed	7	1910.24	Patient refusal	10/0
Completed	70.00	AE (grade 3 dermatitis radiation unrelated to nivo)	7	1910.36	Disease progression	7/1
Completed	68.00	Completed	6	1650.21	AE (grade 2 intracranial hemorrhage unrelated to nivo)	8/6
AE (grade 4 respiratory failure unrelated to nivo)	66.00	Completed	8	2185.95	Completed	10/7
Patient refusal	38.00	Patient refusal	4	1145.62	Patient refusal	2/0
Arm 4: RT + nivo (n = 10)						
Completed	70.00				Completed	10/7
Completed	70.00				Completed	10/7
Completed	70.00				Completed	10/7
Completed	70.00				Disease progression	10/3
Completed	70.00				Disease progression	9/0
Completed	70.00				Disease progression	6/0
Completed	70.00				AE (grade 3 mucositis oral; grade 2 fatigue; both related to nivo)	9/6

RT		Cis/cetux			Nivo	
Reason ended	**Total dose (Gy)**	**Reason ended**	**Number of doses**	**Total dose (mg/m^2)**	**Reason ended**	**Number of doses (concurrent/adjuvant)**
Completed	70.00				AE (grade 3 fatigue related to nivo; grade 3 mucositis oral unrelated to nivo)	3/0
Completed	70.00				Death (ventricular tachycardia unrelated to treatment)	4/0
Completed	70.00				Patient refusal	8/5

Abbreviations: AE = adverse events; cetux = cetuximab; cis = cisplatin; nivo = nivolumab; NOS = not otherwise specified; q7 = every 7 days or weekly; q21 = every 21 days or every 3 weeks; RT = radiation therapy.