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Nivolumab Plus Ipilimumab Versus EXTREME Regimen as First-Line Treatment for Recurrent/Metastatic Squamous Cell Carcinoma of the Head and Neck: The Final Results of CheckMate 651

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PURPOSE CheckMate 651 (ClinicalTrials.gov identifier: [NCT02741570](https://clinicaltrials.gov/ct2/show/study/NCT02741570)) evaluated first-line nivolumab plus ipilimumab versus EXTREME (cetuximab plus cisplatin/carboplatin plus fluorouracil \leq six cycles, then cetuximab maintenance) in recurrent/metastatic squamous cell carcinoma of the head and neck (R/M SCCHN).

METHODS Patients without prior systemic therapy for R/M SCCHN were randomly assigned 1:1 to nivolumab plus ipilimumab or EXTREME. Primary end points were overall survival (OS) in the all randomly assigned and programmed death-ligand 1 combined positive score (CPS) \geq 20 populations. Secondary end points included OS in the programmed death-ligand 1 CPS \geq 1 population, and progression-free survival, objective response rate, and duration of response in the all randomly assigned and CPS \geq 20 populations.

RESULTS Among 947 patients randomly assigned, 38.3% had CPS \geq 20. There were no statistically significant differences in OS with nivolumab plus ipilimumab versus EXTREME in the all randomly assigned (median: 13.9 v 13.5 months; hazard ratio [HR], 0.95; 97.9% CI, 0.80 to 1.13; $P = .4951$) and CPS \geq 20 (median: 17.6 v 14.6 months; HR, 0.78; 97.51% CI, 0.59 to 1.03; $P = .0469$) populations. In patients with CPS \geq 1, the median OS was 15.7 versus 13.2 months (HR, 0.82; 95% CI, 0.69 to 0.97). Among patients with CPS \geq 20, the median progression-free survival was 5.4 months (nivolumab plus ipilimumab) versus 7.0 months (EXTREME), objective response rate was 34.1% versus 36.0%, and median duration of response was 32.6 versus 7.0 months. Grade 3/4 treatment-related adverse events occurred in 28.2% of patients treated with nivolumab plus ipilimumab versus 70.7% treated with EXTREME.

CONCLUSION CheckMate 651 did not meet its primary end points of OS in the all randomly assigned or CPS \geq 20 populations. Nivolumab plus ipilimumab showed a favorable safety profile compared with EXTREME. There continues to be a need for new therapies in patients with R/M SCCHN.

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INTRODUCTION

Squamous cell carcinomas of the head and neck (SCCHN) are common worldwide, with most patients presenting with advanced disease.^{1,2} Key risk factors are heavy consumption of alcohol and tobacco and human papillomavirus (HPV) infection, which, when detected in tumors, is associated with a favorable prognosis for oropharyngeal SCCHN.³ Overall, > 50% of patients with locally advanced SCCHN treated with multimodal approaches develop recurrence or metastases within

3 years of curative-intent treatment completion.^{4,5} Recurrent/metastatic (R/M) SCCHN is associated with poor prognosis, high levels of morbidity, and deterioration in quality of life.^{1,2,5}

First-line systemic therapy for R/M SCCHN previously relied on agents such as platinum, taxanes, and antimetabolites.^{3,5} In a phase III trial, the EXTREME (cetuximab plus cisplatin/carboplatin plus fluorouracil \leq six cycles, then cetuximab maintenance) regimen significantly improved overall survival (OS) versus

ASSOCIATED CONTENT

See accompanying editorial on page 2134

Appendix

Data Supplement Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

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CONTEXT

Key Objective

Recurrent/metastatic squamous cell carcinoma of the head and neck (SCCHN) is associated with poor prognosis and notable morbidity. The phase III CheckMate 651 study evaluated dual immunotherapy with nivolumab plus ipilimumab versus the EXTREME (cetuximab plus cisplatin/carboplatin plus fluorouracil \leq six cycles, then cetuximab maintenance) regimen as first-line treatment for patients with recurrent/metastatic SCCHN.

Knowledge Generated

First-line nivolumab plus ipilimumab did not result in a significant improvement in overall survival versus EXTREME in all randomly assigned or programmed death-ligand 1 combined positive score \geq 20 populations. Nivolumab plus ipilimumab had a favorable safety profile versus EXTREME.

Relevance (G.K. Schwartz)

Use of immunotherapy in the treatment of SCCHN is still evolving, with a continued unmet need for first-line regimens that provide durable clinical benefit with tolerable safety. Further research is needed to determine the utility of dual immunotherapy as a treatment option for SCCHN and identify novel biomarkers to predict benefit with immunotherapy.*

*Relevance section written by JCO Associate Editor Gary K. Schwartz, MD.

chemotherapy alone (median OS, 10.1 v 7.4 months).^{6,7} However, responses with EXTREME were not durable, and treatment was not generally well tolerated, with an increased incidence of grade 3/4 skin reactions, sepsis, hypomagnesemia, and anorexia. The TPEX regimen (cetuximab combined with docetaxel and cisplatin) showed no OS benefit versus EXTREME (median OS, 14.5 v 13.4 months) despite improved compliance and favorable safety.⁸

Interventions targeting programmed death-1 (PD-1) have shifted the standard of care to immunotherapy in both first- and second-line settings for R/M SCCHN.³ Pembrolizumab monotherapy improved OS versus chemotherapy-based regimens in platinum-refractory R/M SCCHN and in the first-line setting for programmed death-ligand 1 (PD-L1)-positive platinum-eligible R/M SCCHN; first-line pembrolizumab plus chemotherapy improved OS in platinum-eligible R/M SCCHN.^{9,10} In CheckMate 141, nivolumab monotherapy improved OS versus investigator's choice of chemotherapy in patients with platinum-refractory R/M SCCHN and in a subgroup of patients who progressed \leq 6 months of platinum-based chemotherapy for locally advanced disease (LAD) in the adjuvant or primary setting.¹¹⁻¹³ These immunotherapy-based regimens are recommended by the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (NCCN Guidelines) and European Society for Medical Oncology (ESMO) Guidelines as treatment options for appropriate patients with R/M SCCHN.^{4,14} Despite advances in the treatment of R/M SCCHN, there persists an unmet need to improve clinical outcomes.

The immune checkpoint inhibitors nivolumab (a fully human anti-PD-1 antibody) and ipilimumab (a fully human anti-cytotoxic T-lymphocyte-associated antigen 4 antibody) have distinct but complementary mechanisms of action¹⁵ and

have shown OS benefit and durable responses in several solid tumors, including non-small-cell lung cancer, malignant pleural mesothelioma, melanoma, renal cell carcinoma, and esophageal squamous cell carcinoma.¹⁶⁻²¹ Here, we report the results from CheckMate 651 (ClinicalTrials.gov identifier: [NCT02741570](https://clinicaltrials.gov/ct2/show/study/NCT02741570)), a randomized, open-label, phase III trial that evaluated first-line nivolumab plus ipilimumab versus EXTREME in platinum-eligible R/M SCCHN.

METHODS

Patients

Eligible patients were age 18 years or older with histologically confirmed R/M SCCHN of the oral cavity, oropharynx, hypopharynx, or larynx not amenable to curative therapy, measurable disease per RECIST v1.1,²² documented tumor PD-L1 and HPV (determined by p16 for oropharyngeal cancer [OPC]) status, Eastern Cooperative Oncology Group performance status 0-1, no prior systemic therapy in the R/M setting, and no prior treatment with epidermal growth factor receptor inhibitors. Patients who received prior chemotherapy as part of multimodal therapy for LAD were eligible if disease progression did not occur \leq 6 months of definitive treatment.

Study Design and Treatment

Patients were randomly assigned 1:1 to nivolumab (3 mg/kg intravenously once every 2 weeks) plus ipilimumab (1 mg/kg intravenously once every 6 weeks) or EXTREME.⁶ Stratification factors were tumor PD-L1 expression ($<$ 1% v \geq 1%), p16 status (OPC p16-positive v p16-negative/non-OPC), and prior chemotherapy for LAD (yes v no). Treatment continued until disease progression, unacceptable toxicity, withdrawal of consent, or for \leq 2 years on immunotherapy.

Crossover between treatment arms was not permitted. Additional details on study design, treatment, assessments, and statistical analyses are included in the Data Supplement (online only).

CheckMate 651 was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice guidelines. Institutional review boards or independent ethics committees approved the study Protocol (online only) and patient consent form at each site before study initiation. All patients provided written informed consent.

End Points and Assessments

The primary end points were OS in the all randomly assigned and PD-L1 combined positive score (CPS) ≥ 20 populations. PD-L1 staining was performed on tumor tissue using the Dako PD-L1 immunohistochemistry 28-8 pharmDx assay.²³ Tumor PD-L1 expression was defined as the percentage of tumor cells exhibiting plasma membrane staining at any intensity; CPS was calculated as the number of PD-L1–staining cells, including tumor cells, lymphocytes, and macrophages, divided by the total number of viable tumor cells $\times 100$. A key secondary end point was OS in patients with CPS ≥ 1 . Other secondary end points were blinded independent central review–assessed progression-free survival (PFS), objective response rate (ORR), and duration of response (DOR; assessed in patients with complete/partial responses) in the all randomly assigned and CPS ≥ 20 populations.

Exploratory end points included OS subgroup analysis, blinded independent central review–assessed PFS, ORR, and DOR in patients with CPS ≥ 1 , safety, and tolerability. Tumor progression and response were assessed by RECIST v1.1 using computed tomography or magnetic resonance imaging. Safety was assessed in all patients who received ≥ 1 dose of any treatment component. Adverse events (AEs) were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events v4.0. Patient-reported outcomes were assessed as exploratory end points in the all randomly assigned and CPS ≥ 20 populations. Symptom deterioration in the Functional Assessment of Cancer Therapy – Head and Neck (FACT-H&N) was assessed using a 10-item Symptom Index (FHNSI-10), and overall self-reported health status was evaluated using the 3-level version of the EQ-5D (EQ-5D-3L) 100-point visual analog scale.^{24,25}

Statistical Analyses

OS, PFS, and DOR were estimated by the Kaplan-Meier method. OS in the all randomly assigned and CPS ≥ 20 populations (primary end points) were tested in parallel, with equal overall two-sided $\alpha = .025$ (incorporating the O'Brien-Fleming α spending function) using stratified log-rank test. A statistical testing hierarchy was used for OS assessment in the all randomly assigned, CPS ≥ 20 , and CPS ≥ 1 populations. OS in CPS ≥ 1 (secondary end

point) was to be tested at the same α level as CPS ≥ 20 only if OS in CPS ≥ 20 was statistically significant. If OS in CPS ≥ 20 was not statistically significant, OS in CPS ≥ 1 was to be analyzed using descriptive statistics. Hazard ratio (HR) and the corresponding two-sided $100 \times (1 - \text{adjusted } \alpha)\%$ CI were estimated using a stratified Cox proportional hazards model. PFS was analyzed using a stratified Cox proportional hazards model. ORR and associated CIs were computed using the Clopper and Pearson method. FHNSI-10 and EQ-5D-3L analyses included patients with baseline and ≥ 1 postbaseline on-treatment assessments.

A protocol-defined sensitivity analysis was conducted to assess the impact of nonproportional hazards on OS in the event of curve crossing. In addition, a post hoc sensitivity analysis was conducted to evaluate the effect of subsequent immunotherapy (second-line or later) on OS.

RESULTS

Patients and Treatment

In CheckMate 651, 947 patients were randomly assigned to nivolumab plus ipilimumab ($n = 472$) or EXTREME ($n = 475$); 468 and 441 patients received ≥ 1 dose of treatment, respectively. The median age (range) was 61 years (24-86) in the nivolumab plus ipilimumab arm and 62 years (29-86) in the EXTREME arm; 80.5% and 83.6% were male, 76.3% and 77.7% were current/former smokers, 39.2% and 37.5% had CPS ≥ 20 , and 57.2% and 57.7% had tumor PD-L1 expression $\geq 1\%$, respectively. HPV status was OPC p16-positive in 19.9% and 18.5%, and 53.6% and 51.8% had received prior chemotherapy for LAD, respectively. Similar distributions were reported in the CPS ≥ 20 population (Table 1).

At database lock (June 21, 2021), the minimum and median follow-up was 27.3 and 39.1 months, respectively. In the nivolumab plus ipilimumab arm, no patients remained on treatment, with 8.5% completing the full 2 years of treatment; in the EXTREME arm, 1.6% remained on treatment (Fig 1). In all randomly assigned patients, the median duration of therapy was 3.8 months (range < 0.1 -24.0) with nivolumab plus ipilimumab versus 5.0 months (range < 0.1 -50.7) with EXTREME. A median of eight doses (range, 1-53) of nivolumab and three doses (range, 1-18) of ipilimumab were administered. In the EXTREME arm, 34% of patients received cisplatin, 54% received carboplatin, and 11% received cisplatin and carboplatin during treatment. A median of 4.0 doses (range, 1-6) of cisplatin and 5.0 doses (range, 1-6) of carboplatin were administered. Overall, 52.8% of patients received cetuximab maintenance therapy. Subsequent systemic therapy was administered in 49.2% (nivolumab plus ipilimumab) and 60.2% (EXTREME) of patients with 8.5% and 46.3%, respectively, receiving subsequent immunotherapy (mostly nivolumab), 42.2%

TABLE 1. Baseline Characteristics in the All Randomly Assigned and PD-L1 CPS \geq 20 Populations

Characteristic	All Randomly Assigned		PD-L1 CPS \geq 20	
	Nivolumab Plus Ipilimumab (n = 472)	EXTREME (n = 475)	Nivolumab Plus Ipilimumab (n = 185)	EXTREME (n = 178)
Age, years, median (range)	61 (24-86)	62 (29-86)	61 (30-83)	61 (31-86)
Male, No. (%)	380 (80.5)	397 (83.6)	147 (79.5)	137 (77.0)
ECOG PS, ^a No. (%)				
0	152 (32.2)	173 (36.4)	64 (34.6)	66 (37.1)
1	318 (67.4)	300 (63.2)	119 (64.3)	110 (61.8)
Current or former smoker, No. (%)	360 (76.3)	369 (77.7)	133 (71.9)	139 (78.1)
Disease status, ^b No. (%)				
Locally recurrent	133 (28.2)	170 (35.8)	59 (31.9)	62 (34.8)
Locally recurrent and metastatic	152 (32.2)	114 (24.0)	59 (31.9)	48 (27.0)
Metastatic	186 (39.4)	190 (40.0)	67 (36.2)	68 (38.2)
Primary site, ^c No. (%)				
Oral cavity	127 (26.9)	132 (27.8)	71 (38.4)	58 (32.6)
Oropharynx	202 (42.8)	194 (40.8)	72 (38.9)	71 (39.9)
Hypopharynx	45 (9.5)	56 (11.8)	11 (5.9)	20 (11.2)
Larynx	98 (20.8)	92 (19.4)	31 (16.8)	29 (16.3)
OPC p16-positive, ^{d,e} No. (%)	94 (19.9)	88 (18.5)	33 (17.8)	38 (21.3)
Prior chemotherapy for LAD, ^{e,f} No. (%)	253 (53.6)	246 (51.8)	89 (48.1)	99 (55.6)
Tumor PD-L1 expression, ^{e,g} No. (%)				
< 1% or nonevaluable	201 (42.6)	201 (42.3)	14 (7.6)	17 (9.6)
\geq 1%	270 (57.2)	274 (57.7)	171 (92.4)	161 (90.4)
PD-L1 CPS, ^h No. (%)				
< 1	92 (19.5)	86 (18.1)	—	—
\geq 1	355 (75.2)	372 (78.3)	—	—
\geq 20	185 (39.2)	178 (37.5)	185 (100.0)	178 (100.0)

Abbreviations: CPS, combined positive score; ECOG PS, Eastern Cooperative Oncology Group performance status; EXTREME, cetuximab plus cisplatin/carboplatin plus fluorouracil \leq six cycles, then cetuximab maintenance; LAD, locally advanced disease; OPC, oropharyngeal cancer; PD-L1, programmed death-ligand 1.

^aECOG PS of 2 was reported in 2 and 1 patients in the nivolumab plus ipilimumab and EXTREME arms, respectively; ECOG PS was not reported in 1 patient in the EXTREME arm.

^bDisease status was not reported in 1 patient each in the nivolumab plus ipilimumab and EXTREME arms of the all randomly assigned population.

^cPrimary site was reported as *other* in 1 patient in the EXTREME arm of the all randomly assigned population.

^dp16 status was not reported in 1 patient each in the nivolumab plus ipilimumab and EXTREME arms of the all randomly assigned population.

^ePer interactive response technology.

^fAdjuvant, neoadjuvant, or multimodal therapy for LAD.

^gTumor PD-L1 expression was not reported in 1 patient in the nivolumab plus ipilimumab arm of the all randomly assigned population.

^h5.3% and 3.6% of all randomly assigned patients in the nivolumab plus ipilimumab arm and EXTREME arm, respectively, were nonevaluable for PD-L1 CPS.

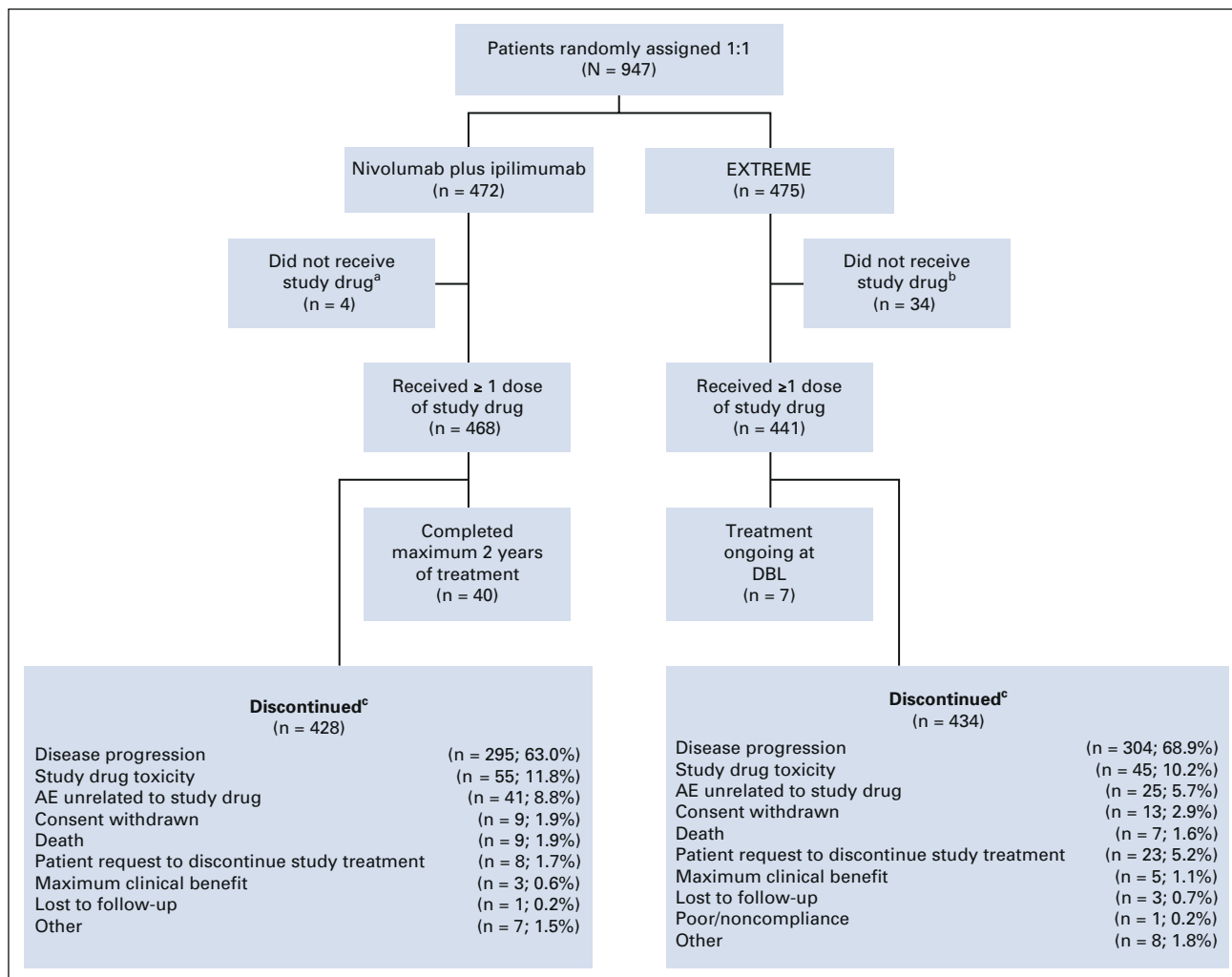


FIG 1. CONSORT diagram of patient disposition in all randomly assigned patients. Minimum follow-up: 27.3 months; database lock: June 21, 2021. ^aPatients who were randomly assigned and did not receive nivolumab plus ipilimumab treatment owing to patient no longer meeting study criteria (n = 3) and AEs unrelated to study drug (n = 1). ^bPatients who were randomly assigned and did not receive EXTREME treatment owing to consent withdrawal (n = 18), patient no longer meeting study criteria (n = 6), loss to follow-up (n = 2), patient request (n = 2), disease progression (n = 1), death (n = 1), poor compliance or noncompliance (n = 1), and other (n = 3). ^cData are reported as the number of patients discontinued per reason/number of treated patients in each arm (%). AE, adverse event; DBL, database lock; EXTREME, cetuximab plus cisplatin/carboplatin plus fluorouracil ≤ six cycles, then cetuximab maintenance.

and 16.2% receiving platinum-based chemotherapy, and 27.3% and 12.8% receiving cetuximab. A similar proportion of patients received subsequent therapy in the CPS ≥ 20 population (Data Supplement).

Efficacy

The median OS was 13.9 months (95% CI, 12.1 to 15.8) with nivolumab plus ipilimumab versus 13.5 months (95% CI, 12.6 to 15.2) with EXTREME in all randomly assigned patients and 17.6 months (95% CI, 13.8 to 22.0) versus 14.6 months (95% CI, 12.3 to 16.0) in the CPS ≥ 20 population. The primary end points of OS with nivolumab plus ipilimumab versus EXTREME were not met in the all randomly assigned (HR, 0.95; 97.9% CI, 0.80 to 1.13; $P = .4951$; Fig 2A) or CPS ≥ 20 (HR, 0.78; 97.51% CI,

0.59 to 1.03; $P = .0469$; Fig 2B) populations. OS with nivolumab plus ipilimumab versus EXTREME was similar, regardless of cisplatin or carboplatin administration, in both the all randomly assigned (HR, 1.04; 95% CI, 0.85 to 1.26, and 0.94; 95% CI, 0.79 to 1.11) and CPS ≥ 20 (HR, 0.84; 95% CI, 0.60 to 1.19, and 0.82; 95% CI, 0.62 to 1.10) populations. In the CPS ≥ 1 population, the median OS was 15.7 months (95% CI, 13.7 to 18.8) with nivolumab plus ipilimumab versus 13.2 months (95% CI, 11.1 to 14.6) with EXTREME (HR, 0.82; 95% CI, 0.69 to 0.97; Fig 2C); P value was not calculated on the basis of the protocol-specified testing hierarchy.

As late benefit is often observed with immunotherapy versus chemotherapy-based regimens, the impact of

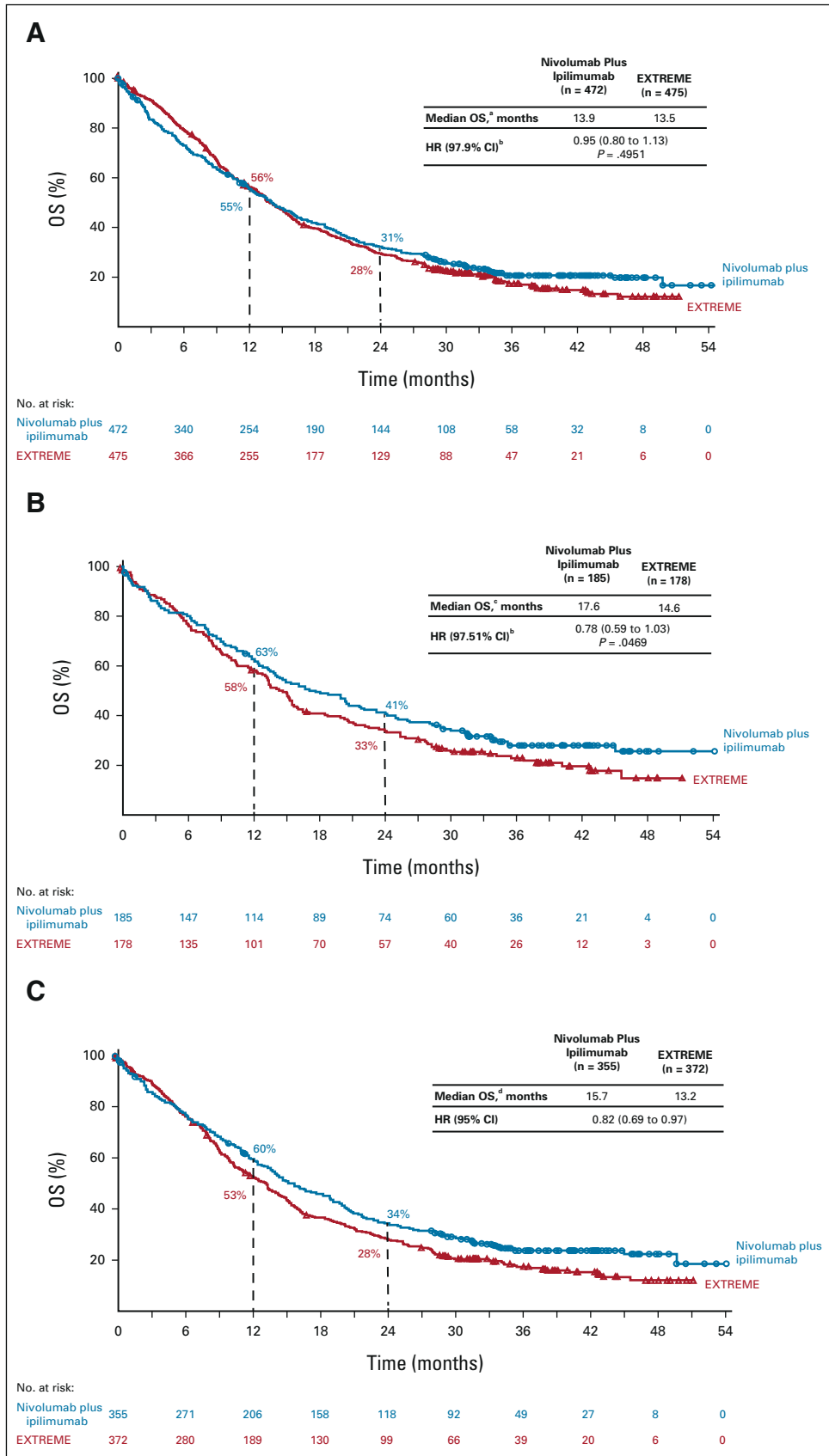


FIG 2. OS in the (A) all randomly assigned population, (B) PD-L1 CPS \geq 20 population, and (C) PD-L1 CPS \geq 1 population. Minimum follow-up: 27.3 months. ^a95% CI, 12.1 to 15.8 (continued on following page)

FIG 2. (Continued). (nivolumab plus ipilimumab) and 12.6 to 15.2 (EXTREME). ^bCI's are adjusted on the basis of the final α levels for each primary end point. ^c95% CI, 13.8 to 22.0 (nivolumab plus ipilimumab) and 12.3 to 16.0 (EXTREME). ^d95% CI, 13.7 to 18.8 (nivolumab plus ipilimumab) and 11.1 to 14.6 (EXTREME). CPS, combined positive score; EXTREME, cetuximab plus cisplatin/carboplatin plus fluorouracil \leq six cycles, then cetuximab maintenance; HR, hazard ratio; OS, overall survival; PD-L1, programmed death-ligand 1.

nonproportional hazards on OS was analyzed; the results showed no statistically significant benefit with nivolumab plus ipilimumab versus EXTREME in the all randomly assigned or CPS \geq 20 populations (Data Supplement).

Given the larger proportion of patients in the EXTREME arm receiving subsequent immunotherapy (46% v 9% in the nivolumab plus ipilimumab arm), an ad hoc analysis was performed to adjust for its impact on the primary outcome.

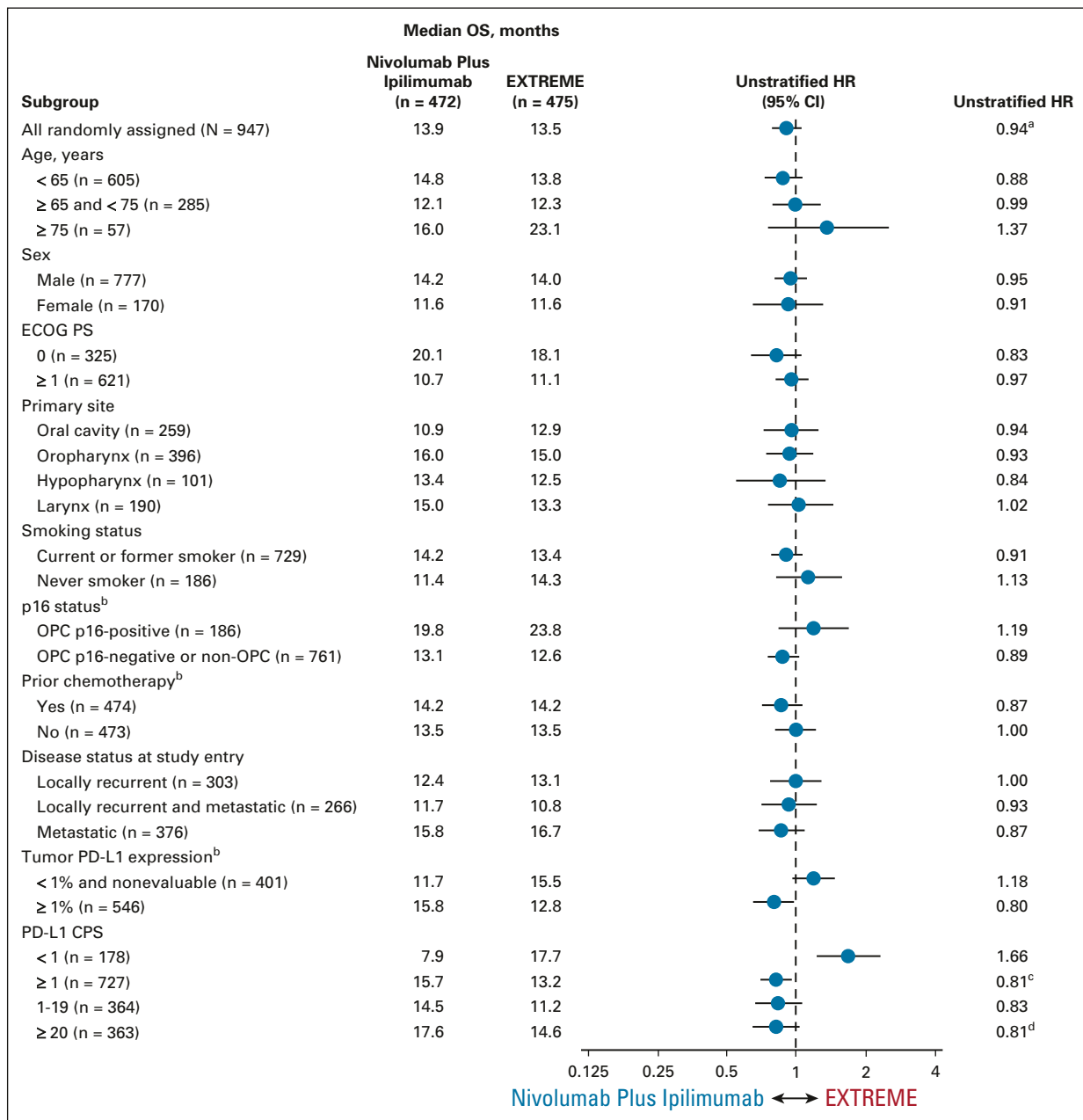


FIG 3. OS subgroup analyses in the all randomly assigned population. ^aStratified HR, 0.95. ^bPer interactive response technology. ^cStratified HR, 0.82. ^dStratified HR, 0.78. CPS, combined positive score; ECOG PS, Eastern Cooperative Oncology Group performance status; EXTREME, cetuximab plus cisplatin/carboplatin plus fluorouracil \leq six cycles, then cetuximab maintenance; HR, hazard ratio; OPC, oropharyngeal cancer; OS, overall survival; PD-L1, programmed death-ligand 1.

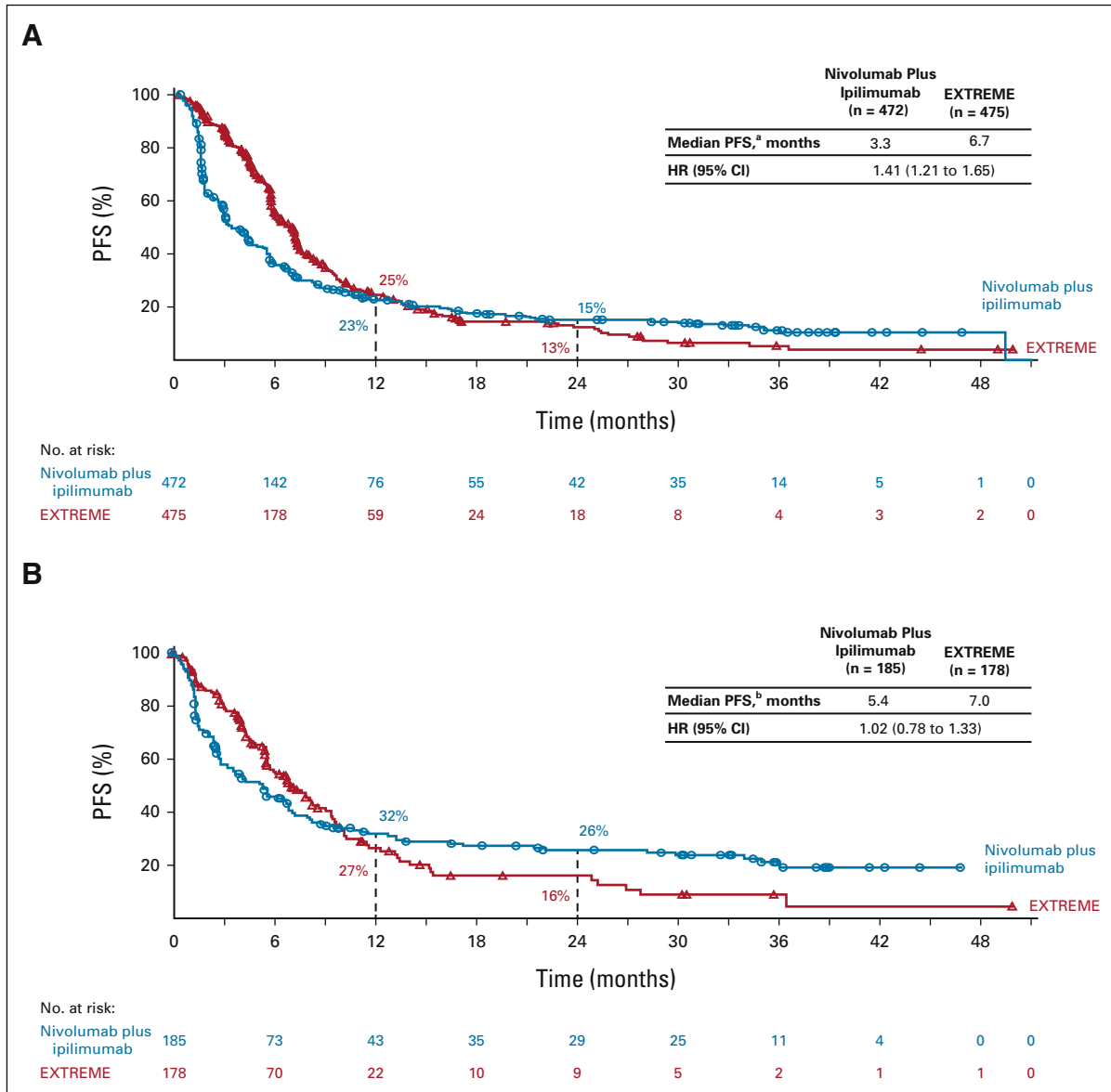


FIG 4. PFS by BICR in the (A) all randomly assigned and (B) PD-L1 CPS \geq 20 populations; DOR (in patients with complete or partial responses) by BICR in the (C) all randomly assigned and (D) PD-L1 CPS \geq 20 populations. Minimum follow-up: 27.3 months. ^a95% CI, 2.8 to 4.2 (nivolumab plus ipilimumab) and 5.8 to 7.0 (EXTREME). ^b95% CI, 3.1 to 6.9 (nivolumab plus ipilimumab) and 5.6 to 8.7 (EXTREME). ^c95% CI, 9.7 to 29.4 (nivolumab plus ipilimumab) and 5.4 to 7.0 (EXTREME). ^d95% CI, 12.1 to NR (nivolumab plus ipilimumab) and 5.6 to 10.1 (EXTREME). BICR, blinded independent central review; CPS, combined positive score; DOR, duration of response; EXTREME, cetuximab plus cisplatin/carboplatin plus fluorouracil \leq six cycles, then cetuximab maintenance; HR, hazard ratio; NR, not reached; PD-L1, programmed death-ligand 1; PFS, progression-free survival. (continued on following page)

Adjusting both treatment arms, the analysis showed a median OS of 12.4 months with nivolumab plus ipilimumab versus 10.8 months with EXTREME (HR, 0.80; 95% CI, 0.68 to 0.92; Data Supplement) in the all randomly assigned population and 14.1 versus 11.7 months (HR, 0.71; 95% CI, 0.55 to 0.91; Data Supplement) in the CPS \geq 20 population.

Exploratory analyses by baseline characteristics showed no notable difference in median OS across treatment arms in most subgroups in the all randomly assigned population (Fig 3). Generally, similar results were noted

across most subgroups in the CPS \geq 20 population (Data Supplement).

Median PFS was shorter with nivolumab plus ipilimumab versus EXTREME in the all randomly assigned (median, 3.3 months [95% CI, 2.8 to 4.2] v 6.7 months [95% CI, 5.8 to 7.0]; HR, 1.41 [95% CI, 1.21 to 1.65]; Fig 4A), CPS \geq 20 (median [95% CI]: 5.4 [3.1 to 6.9] v 7.0 [5.6 to 8.7] months; HR, 1.02 [95% CI, 0.78 to 1.33]; Fig 4B), and CPS \geq 1 (median, 4.2 months [95% CI, 2.9 to 5.4] v 6.1 months [95% CI, 5.6 to 7.0]; HR, 1.23 [95% CI, 1.03 to 1.47]; Data

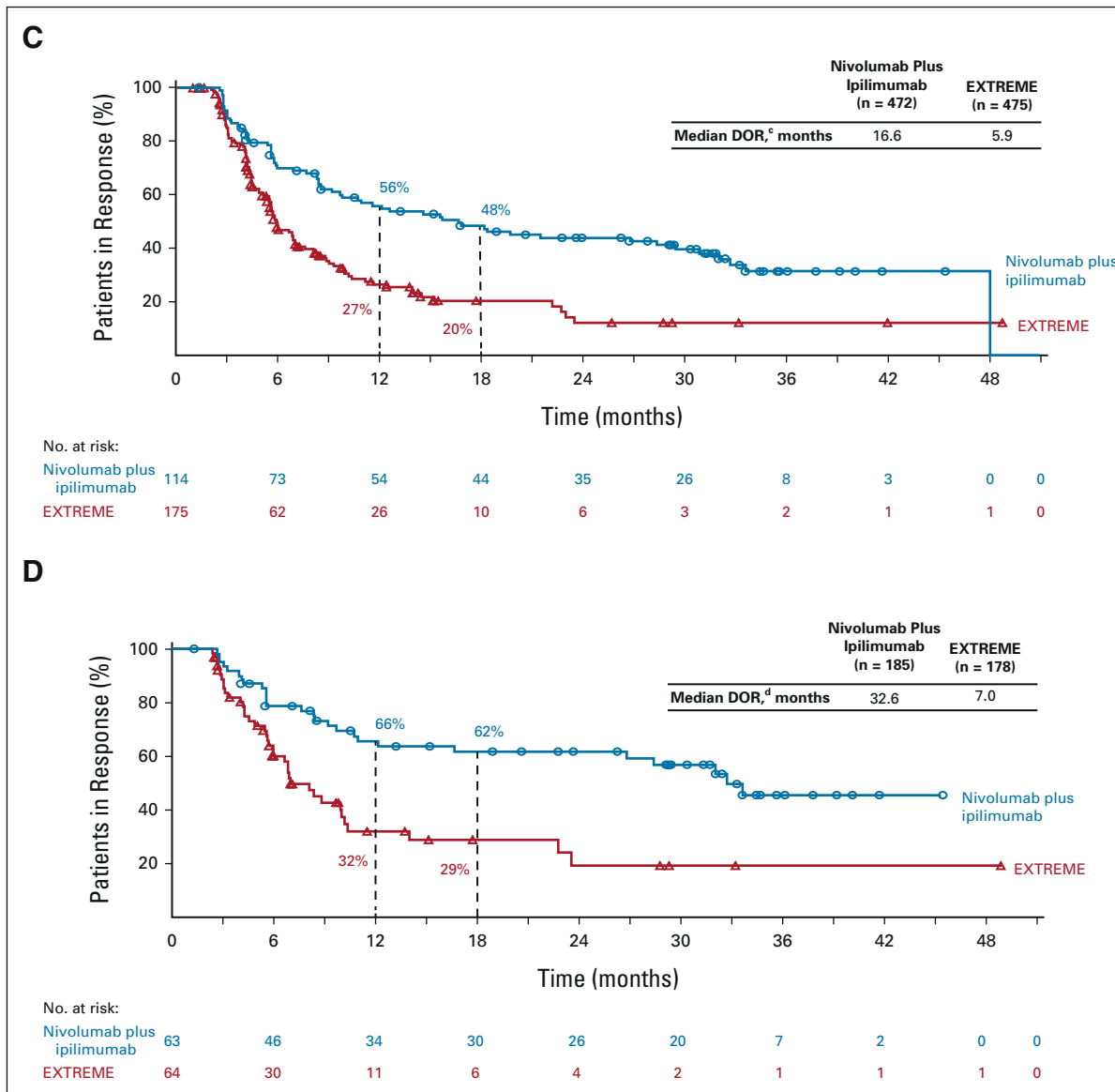


FIG 4. (Continued).

Supplement) populations. The ORR was 24.2% (95% CI, 20.4 to 28.3) with nivolumab plus ipilimumab versus 36.8% (95% CI, 32.5 to 41.4) with EXTREME in all randomly assigned patients and 34.1% (95% CI, 27.3 to 41.4) versus 36.0% (95% CI, 28.9 to 43.5) in the CPS \geq 20 population (Data Supplement); complete response rates were 7.2% versus 4.6% and 12.4% versus 7.3%, respectively. The median DOR was 16.6 months with nivolumab plus ipilimumab versus 5.9 months with EXTREME (all randomly assigned; Fig 4C) and 32.6 versus 7.0 months (CPS \geq 20; Fig 4D). Tumor response data for the CPS \geq 1 population are summarized in the Data Supplement.

Safety

Any-grade and grade 3/4 treatment-related AEs (TRAEs) were reported in 72.2% and 28.2% (nivolumab plus ipilimumab)

versus 97.5% and 70.7% (EXTREME) of treated patients (Table 2). Any-grade and grade 3/4 TRAEs leading to discontinuation of any component of the regimen were reported in 12.4% and 9.6% versus 12.9% and 8.8% of patients, respectively. The most common any-grade TRAEs were fatigue (18.2%), pruritus (15.0%), and hypothyroidism (14.1%) with nivolumab plus ipilimumab and nausea (44.7%), rash (38.3%), and anemia (34.9%) with EXTREME (Table 2). Any-grade and grade 3/4 serious TRAEs were reported in 15.8% and 12.2% (nivolumab plus ipilimumab) versus 27.7% and 23.8% (EXTREME); treatment-related deaths were reported in 1.3% versus 1.8% of patients, respectively.

The most common any-grade immune-mediated AEs (IMAEs) with nivolumab plus ipilimumab were hypothyroidism/thyroiditis (16.0%), rash (12.6%), and

TABLE 2. Incidence of TRAEs in All Treated Patients

TRAE ^a	Nivolumab Plus Ipilimumab (n = 468), No. (%)		EXTREME (n = 441), No. (%)	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Any TRAEs	338 (72.2)	132 (28.2)	430 (97.5)	312 (70.7)
TRAEs leading to discontinuation of any component of the regimen ^{b,c}	58 (12.4)	45 (9.6)	57 (12.9)	39 (8.8)
Serious TRAEs	74 (15.8)	57 (12.2)	122 (27.7)	105 (23.8)
Treatment-related deaths	6 (1.3) ^d		8 (1.8) ^e	
TRAEs occurring in ≥ 10% of patients in either treatment arm				
Fatigue	85 (18.2)	7 (1.5)	123 (27.9)	10 (2.3)
Pruritus	70 (15.0)	3 (0.6)	34 (7.7)	1 (0.2)
Hypothyroidism	66 (14.1)	2 (0.4)	3 (0.7)	0
Rash	65 (13.9)	8 (1.7)	169 (38.3)	28 (6.3)
Diarrhea	49 (10.5)	8 (1.7)	100 (22.7)	10 (2.3)
Asthenia	44 (9.4)	3 (0.6)	87 (19.7)	11 (2.5)
Nausea	32 (6.8)	0	197 (44.7)	19 (4.3)
Decreased appetite	23 (4.9)	1 (0.2)	93 (21.1)	7 (1.6)
Dry skin	17 (3.6)	0	71 (16.1)	5 (1.1)
Anemia	16 (3.4)	2 (0.4)	154 (34.9)	54 (12.2)
Weight decreased	16 (3.4)	0	44 (10.0)	3 (0.7)
Vomiting	16 (3.4)	0	96 (21.8)	9 (2.0)
Constipation	9 (1.9)	0	57 (12.9)	1 (0.2)
Mucosal inflammation	8 (1.7)	1 (0.2)	128 (29.0)	31 (7.0)
Stomatitis	8 (1.7)	0	98 (22.2)	18 (4.1)
Dermatitis acneiform	7 (1.5)	0	147 (33.3)	21 (4.8)
Hypomagnesemia	6 (1.3)	0	117 (26.5)	21 (4.8)
Neutropenia	5 (1.1)	3 (0.6)	126 (28.6)	71 (16.1)
Neutrophil count decreased	3 (0.6)	0	65 (14.7)	43 (9.8)
Hypokalemia	2 (0.4)	1 (0.2)	70 (15.9)	31 (7.0)
Thrombocytopenia	2 (0.4)	1 (0.2)	102 (23.1)	36 (8.2)
Platelet count decreased	1 (0.2)	0	57 (12.9)	17 (3.9)
Skin fissures	1 (0.2)	0	60 (13.6)	4 (0.9)
Paronychia	0	0	85 (19.3)	7 (1.6)

Abbreviations: EXTREME, cetuximab plus cisplatin/carboplatin plus fluorouracil ≤ six cycles, then cetuximab maintenance; TRAE, treatment-related adverse event.

^aTRAEs included those reported between first dose and 30 days after the last dose of study drug.

^bIn the event of discontinuation of ipilimumab treatment, nivolumab treatment could continue; however, continuation of ipilimumab after discontinuation of nivolumab was not allowed.

^cTRAEs led to discontinuation of ipilimumab treatment only in 22 patients.

^dTwo due to pneumonitis, two due to hepatitis, one due to tumor lysis syndrome, and one due to disseminated intravascular coagulation.

^eFive due to sepsis, two due to pneumonia, and one due to acute respiratory syndrome.

hyperthyroidism (6.8%); grade 3/4 events were uncommon (Data Supplement). Most events occurred within the first 5 months of treatment (Data Supplement). The median duration of corticosteroid use for IMAEs ranged from 0.3 (hypophysitis) to 6.0 (hypothyroidism/thyroiditis) weeks; most nonendocrine IMAEs resolved with corticosteroids ≥ 40 mg once daily. Times to onset and resolution of IMAEs,

including treatment with immune-modulating medications, are summarized in the Data Supplement.

Patient-Reported Outcomes

Completion rates for patient-reported outcome assessments were > 80% at baseline. In the CPS ≥ 20 population, nivolumab plus ipilimumab versus EXTREME tended to

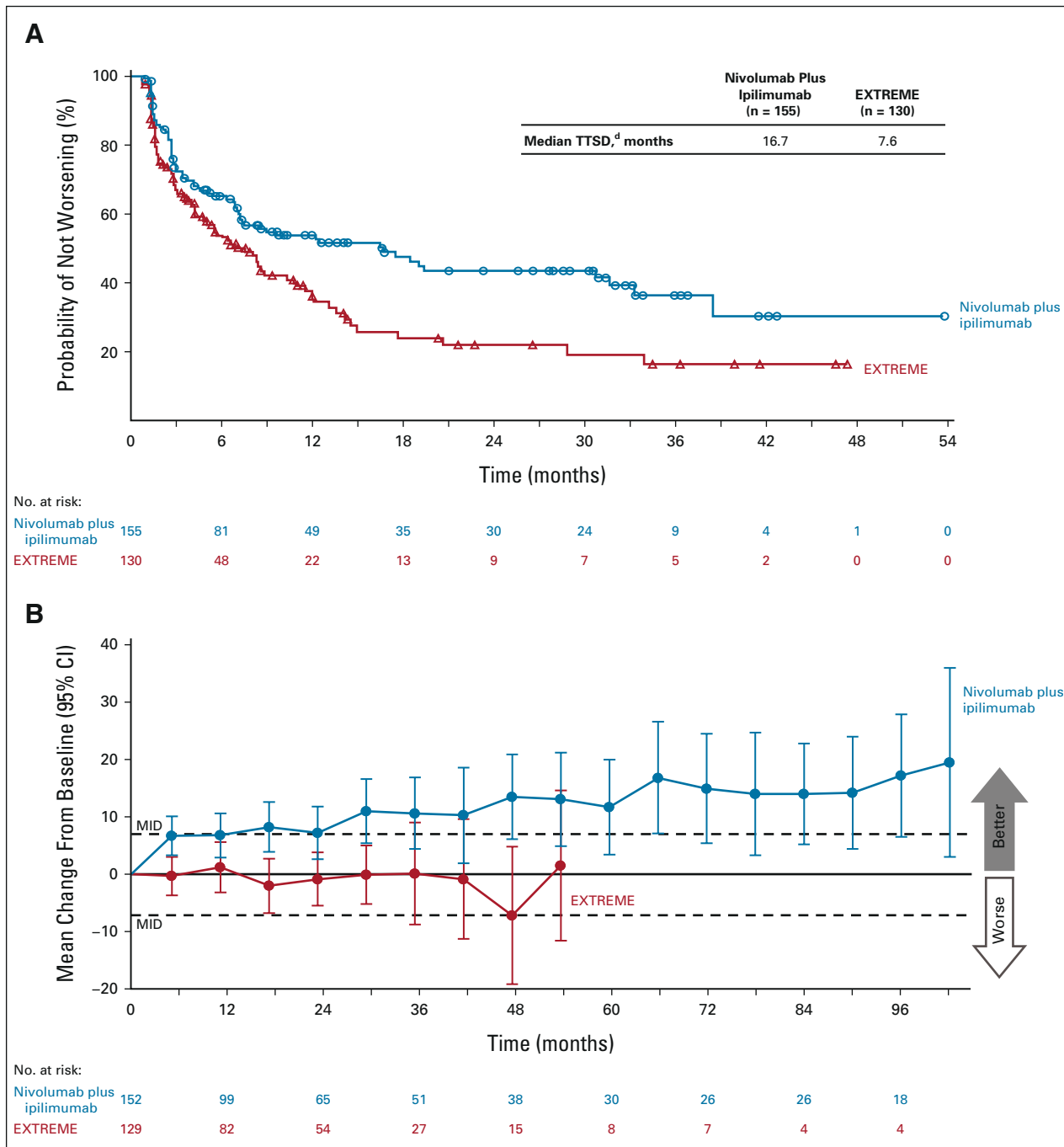


FIG 5. (A) Time to symptom deterioration (FHNSI-10)^a and (B) overall self-rated health status (EQ-5D-3L VAS)^{b,c} in the PD-L1 CPS \geq 20 population. Minimum follow-up: 27.3 months. ^aTime to symptom deterioration is defined as the time from random assignment to first clinically meaningful decline (reduction of \geq 3 points) from baseline in FHNSI-10 score.²⁶ ^bMean (95% CI) change from baseline; horizontal reference line indicates MID = 7-point change on EQ-5D-3L VAS.²⁷ ^cOnly on-treatment time points with data for \geq 10 patients in either treatment group are shown, not adjusted for multiplicity. ^d95% CI, 7.4 to 31.6 (nivolumab plus ipilimumab) and 4.3 to 10.9 (EXTREME). CPS, combined positive score; EQ-5D-3L VAS, EQ-5D 3-level version visual analog scale; EXTREME, cetuximab plus cisplatin/carboplatin plus fluorouracil \leq six cycles, then cetuximab maintenance; FHNSI-10, Functional Assessment of Cancer Therapy Head and Neck Cancer Symptom 10-Item Index; MID, minimally important difference; PD-L1, programmed death-ligand 1; TTSD, time to symptom deterioration.

delay symptom deterioration (per FHNSI-10, median time to symptom deterioration: 16.7 v 7.6 months, respectively; Fig 5A) and resulted in clinically meaningful improvement in overall self-rated health status (per EQ-5D-3L visual analog

scale, mean changes in scores from baseline exceeded the minimally important difference after week 24; Fig 5B). The results were similar, but less pronounced, in the all randomly assigned population (Data Supplement).

DISCUSSION

CheckMate 651 was a large phase III study designed to evaluate first-line nivolumab plus ipilimumab versus EXTREME in platinum-eligible R/M SCCHN. This study did not meet its primary end points of OS in the all randomly assigned or PD-L1 CPS \geq 20 populations. The median OS was 13.9 months (95% CI, 12.1 to 15.8) with nivolumab plus ipilimumab versus 13.5 months (95% CI, 12.6 to 15.2) with EXTREME in the all randomly assigned population and 17.6 months (95% CI, 13.8 to 22.0) versus 14.6 months (95% CI, 12.3 to 16.0) in the CPS \geq 20 population and did not reach statistical significance in either population. Notably, the number of patients with CPS \geq 20 ($n = 363$) was smaller than the number of events ($n = 372$) required to maintain planned statistical power for the primary end point, resulting in a loss of statistical power to demonstrate a difference. ORR was higher with EXTREME in the all randomly assigned population but similar in both treatment arms of the CPS \geq 20 population (with higher proportions of complete responses with nivolumab plus ipilimumab versus EXTREME in both populations). The median DOR was 32.6 months (nivolumab plus ipilimumab) versus 7.0 months (EXTREME) in the CPS \geq 20 population.

Notably, median OS with EXTREME in the all randomly assigned population of CheckMate 651 was higher (13.5 months [95% CI, 12.6 to 15.2]) than the historically reported range of 10.1 (95% CI, 8.6 to 11.2) to 10.7 (95% CI, 9.3 to 11.7) months for first-line R/M SCCHN^{6,9}; a similar result was reported in the TPEX study in which all patients received a cisplatin-based regimen (median OS with EXTREME, 13.4 months [95% CI, 12.2 to 15.4]).⁸ Although these OS outcomes across studies may be due to differences in patient characteristics, such as disease burden, or differences in study designs, a notable change from previous studies was the increasing availability of subsequent immunotherapy after study discontinuation. With the increasing use of second-line immunotherapy because of regulatory approvals of nivolumab in multiple countries,²⁸⁻³⁰ the results in the EXTREME arm of CheckMate 651 may better reflect contemporary clinical practice versus earlier studies such as KEYNOTE-048 in which fewer patients (25%) in the EXTREME arm received subsequent immunotherapy.⁹ Post hoc sensitivity analyses, conducted in the all randomly assigned and CPS \geq 20 populations to investigate the effect of subsequent immunotherapy on OS, yielded lower median OS versus the primary analyses in both treatment arms. However, the extent of reduction in median OS was greater in the EXTREME arm with a notable reduction in the HRs for OS, indicating that the higher proportion of patients who received subsequent immunotherapy, mostly nivolumab, in the EXTREME arm (46.3% v8.5% in the nivolumab plus ipilimumab arm) may have potentially contributed to the higher-than-expected median OS with EXTREME.

Unlike OS, PFS is not affected by postrandom assignment variables such as subsequent therapy. Median PFS was shorter with nivolumab plus ipilimumab versus EXTREME in the all randomly assigned, CPS \geq 20, or CPS \geq 1 populations. Importantly, median PFS with EXTREME in the all randomly assigned population (6.7 months [95% CI, 5.8 to 7.0]) of CheckMate 651 was higher than that reported previously (ranging from 5.1 months [95% CI, 4.9 to 6.0] to 5.6 months [95% CI, 5.0 to 6.0]), which may be related to differences in the patient populations between the studies.^{6,9} Delayed PFS benefit with nivolumab plus ipilimumab was seen in the CPS \geq 20 population of CheckMate 651, with 26% of patients remaining progression free at 2 years versus 16% with EXTREME. A similar effect was reported in the CPS \geq 20 population of KEYNOTE-048, in which the median PFS was 3.4 months (pembrolizumab) versus 5.0 months (EXTREME), with 1-year PFS rates of 23% and 12%, respectively.⁹

Immunotherapies targeting PD-1, such as nivolumab and pembrolizumab, have demonstrated OS benefits in patients with platinum-refractory or platinum-eligible R/M SCCHN. In CheckMate 141, a post hoc subgroup analysis of nivolumab in patients with R/M SCCHN who experienced disease progression on or \leq 6 months of platinum-based chemotherapy for LAD in the adjuvant or primary setting showed improved OS versus chemotherapy; benefit was maintained at 2-year follow-up.³¹ In KEYNOTE-048, first-line pembrolizumab alone or with chemotherapy demonstrated long-term OS benefit versus EXTREME in patients with platinum-eligible disease with CPS \geq 20 or \geq 1^{9,32}; the median OS was 14.9 months (pembrolizumab) and 14.7 months (pembrolizumab plus chemotherapy) in the CPS \geq 20 population.¹⁰ Although cross-trial comparisons should be approached with caution because of differences in study design and patient populations, the median OS of 17.6 months with nivolumab plus ipilimumab in patients with CPS \geq 20 in CheckMate 651 is the longest reported in this patient population at this time.

Of previous studies evaluating dual immunotherapy in R/M SCCHN, phase III trials KESTREL and EAGLE assessing durvalumab alone or in combination with tremelimumab failed to demonstrate clinical benefit versus chemotherapy in the first- and second-line settings, respectively.^{33,34} In the phase II CheckMate 714 trial (ClinicalTrials.gov identifier: [NCT02823574](https://clinicaltrials.gov/ct2/show/study/NCT02823574)), which compared first-line nivolumab plus ipilimumab versus nivolumab in platinum-refractory or platinum-eligible R/M SCCHN, the primary end point of ORR in the platinum-refractory population was not met (13.2% [95% CI, 8.4 to 19.5] with nivolumab plus ipilimumab v 18.3% [95% CI, 10.6 to 28.4] with nivolumab). ORR in the platinum-eligible population was 20.3% (95% CI, 13.6 to 28.5) versus 29.5% (95% CI, 18.5 to 42.6).³⁵⁻³⁷ Lack of clinical benefit with dual immunotherapy compared with single-agent immunotherapy underscores the need for further research to understand the role of the components of

dual immunotherapy with anti-PD-(L)1 and anticytotoxic T-lymphocyte-associated antigen 4 inhibition in hard-to-treat SCCHN.

The use of immunotherapy in SCCHN is mainly driven by CPS.^{9,38} For patients with CPS \geq 20, pembrolizumab monotherapy is recommended as a first-line treatment option on the basis of high-level evidence. This is also an option for certain patients with CPS \geq 1; regardless of CPS status, patients may receive pembrolizumab plus chemotherapy.^{3,14} Effective treatment options for patients who progress on or are refractory to first-line immunotherapy remain a substantial unmet need that warrants exploration, including novel immunotherapy-based combinations or treatment sequencing in R/M SCCHN.

The nivolumab plus ipilimumab dosing regimen in CheckMate 651 was informed by results from the phase I

CheckMate 012 study in advanced non-small-cell lung cancer, in which nivolumab 3 mg/kg once every 2 weeks plus ipilimumab 1 mg/kg once every 6 weeks resulted in tolerable safety and promising efficacy.³⁹ In CheckMate 651, nivolumab plus ipilimumab demonstrated a favorable safety profile versus EXTREME with a lower frequency of any- and serious-grade 3/4 TRAEs and no unexpected IMAEs. Nivolumab plus ipilimumab improved health-related quality of life with delayed time to symptom deterioration versus EXTREME.

In summary, first-line nivolumab plus ipilimumab did not result in a statistically significant improvement in OS versus EXTREME in platinum-eligible R/M SCCHN in the all randomly assigned or CPS \geq 20 populations. Safety with nivolumab plus ipilimumab was favorable compared with EXTREME.

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EQUAL CONTRIBUTION

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CLINICAL TRIAL INFORMATION

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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DATA SHARING STATEMENT

Data are available upon reasonable request. Bristol Myers Squibb policy on data sharing may be found at <https://www.bms.com/researchers-and-partners/independent-research/data-sharing-request-process.html>.

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The list of CheckMate 651 investigators is listed in [Appendix 1](#) (online only).

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Nivolumab Plus Ipilimumab Versus EXTREME Regimen as First-Line Treatment for Recurrent/Metastatic Squamous Cell Carcinoma of the Head and Neck: The Final Results of CheckMate 651

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