CheckMate 141: 1-Year Update and Subgroup Analysis of Nivolumab as First-line Therapy in Patients With Recurrent/Metastatic Head and Neck Cancer

Running head: CheckMate 141: First-line Nivolumab in R/M SCCHN

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INTRODUCTION

Patients with squamous cell carcinoma of the head and neck (SCCHN) frequently present with advanced disease and receive combined modality therapy [1]. Unfortunately, 10–15% of patients progress within 6 months of platinum-based therapy and have a poor prognosis, with no established standard of care [2-5]. The CheckMate 141 trial investigated nivolumab vs investigator's choice (IC) of therapy in patients with recurrent or metastatic (R/M) SCCHN. Eligible patients had experienced tumor progression or recurrence within 6 months of platinum-based chemotherapy administered in the locally advanced, recurrent, or metastatic disease setting. Nivolumab significantly extended overall survival (OS) compared with IC (hazard ratio [HR], 0.70; 97.73% confidence interval [CI], 0.51–0.96; $p = .01$) in the overall study population [6]. Here, we report outcomes among patients who received nivolumab vs. IC as first-line treatment for R/M SCCHN after progressing on platinum therapy for locally advanced disease in the adjuvant or primary (i.e., with radiation) setting, hereafter referred to as first-line treatment for R/M SCCHN. Updated results with longer follow-up in the overall population are also reported.

METHODS

In the randomized, open-label, phase III CheckMate 141 (NCT02105636) trial [6], patients were randomized 2:1 to nivolumab (3 mg/kg every 2 weeks) or IC (methotrexate, docetaxel, or cetuximab). The primary endpoint was OS; additional endpoints included progression-free survival (PFS), objective response rate (ORR; per Response Evaluation Criteria In Solid Tumors version 1.1), and safety [6]. In the present post hoc analysis, efficacy and safety were assessed in patients receiving nivolumab vs IC as first-line treatment for R/M SCCHN. Updated results in the overall intent-to-treat population, based on a

database lock of September 2016, are also reported. Cox proportional hazards models were used to estimate HRs and CIs.

CheckMate 141 was registered with the National Cancer Institute and approved by the institutional board at each participating site. All patients provided informed consent prior to enrollment.

RESULTS

First-line Treatment for R/M SCCHN

In all, 78 patients (21.6%) received nivolumab (*n* = 52) or IC (*n* = 26) as first-line treatment for R/M SCCHN. The baseline characteristics of these patients (Supplemental Table 1) were similar to those of the overall population [6].

Nivolumab as first-line treatment improved OS vs. IC in patients with R/M SCCHN (median [95% CI], 7.7 [3.1–13.8] vs. 3.3 [2.1–6.4] months; HR [95% CI], 0.56 [0.33–0.95]) (Fig. 1). The 12-month OS rate was 39.2% vs. 15.4%, respectively. Median (95% CI) PFS was 2.3 (1.9–3.3) months for nivolumab and 2.3 (1.7–3.2) months for IC; HR, 0.81; 95% CI, 0.48–1.37. The ORR was 19.2% vs. 11.5%, respectively; time to response was 2.0 months in both arms (Supplemental Table 2). Grade 3–4 treatment-related adverse event (TRAE) rates were 27.5% for nivolumab and 32.0% for IC (Supplemental Table 3).

One-Year Follow-up in the Overall Intent-to-Treat Population

With a minimum follow-up of 11.4 months, 16/240 patients (7%) in the nivolumab arm and 1/121 patients (1%) in the IC arm in the intent-to-treat population were still on treatment (Supplemental Fig. 1). Median (range) duration of therapy was 1.9 (0–24+) months for nivolumab and 1.9 (0–12+) months for

IC. Nivolumab continued to improve OS vs. IC significantly (Fig. 2), with the 18-month OS rate nearly tripled (21.5% vs. 8.3%). OS among subgroups was generally consistent with overall treatment effect (Supplemental Fig. 2). Median (95% CI) PFS was 2.0 (1.9–2.1) months for nivolumab and 2.3 (2.0–3.1) months for IC; HR, 0.87; 95% CI, 0.69–1.11. ORR did not change from the initial analysis [6]; six patients in the nivolumab arm and one patient in the IC arm had a complete response and were alive at last follow-up. As of database lock, three patients were off-study and four patients still on-study had not progressed. Median (range) time to response was 2.1 (1.8–7.4) months for nivolumab vs. 2.0 (1.9–4.6) months for IC. Median (range) duration of response was 9.7 (2.8–20.3+) months vs. 4.0 (1.5+–8.5+) months, respectively.

TRAEs in the overall treated population in the 1-year follow-up were consistent with the initial analysis; longer follow-up identified no new safety signals. Grade 3–4 TRAE rates were 15.3% for nivolumab vs. 36.0% for IC (Supplemental Table 4). Select endocrine TRAEs were more frequent with nivolumab than with IC; none was grade 3–4. Skin-related TRAEs were the most common select TRAEs in both treatment arms.

DISCUSSION

Consistent with outcomes in the overall patient population of CheckMate 141, nivolumab as first-line treatment improved OS and ORR compared with IC in patients with R/M SCCHN. PFS was similar with nivolumab vs. IC, as were rates of high-grade TRAEs. Nivolumab is the only agent to significantly improve survival in a randomized phase III trial for platinum-refractory R/M SCCHN. With a minimum follow-up of 11.4 months in the present analysis, efficacy and safety in the overall intent-to-treat population were similar to results at earlier time points [6].

The current standard of care for first-line treatment of platinum-eligible R/M SCCHN is the EXTREME regimen; however, patients with platinum-refractory SCCHN were not included in the EXTREME trial. Patients eligible for CheckMate 141, who were platinum-refractory due to progression within 6 months of treatment in the primary setting, are generally not candidates for platinum-containing therapies such as EXTREME [7]. Their treatment options are limited to methotrexate, taxanes, or cetuximab—the IC options in the CheckMate 141 trial. Nivolumab as first-line treatment for R/M SCCHN resulted in a 12-month OS of 39% in patients with platinum-refractory disease. Furthermore, quality-of-life benefits were observed with nivolumab vs. IC in CheckMate 141 [8].

Although these data represent a small subgroup of patients, the results support the use of nivolumab as first-line therapy for patients with R/M SCCHN who progressed within 6 months of platinum-based therapy in the adjuvant or primary setting. CheckMate 714 (NCT02823574) is an ongoing, randomized, double-blind, phase II study designed to evaluate the clinical benefit of adding anti–CTLA-4 targeted therapy (ipilimumab) to nivolumab for patients with platinum-refractory or platinum-eligible R/M SCCHN [9]. Nivolumab plus ipilimumab is being evaluated in CheckMate 651 as first-line therapy for platinum-eligible R/M disease vs. EXTREME (NCT02741570) [10].

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FIGURE LEGENDS

Figure 1. OS (A) and treatment effect on OS (B) among patients randomized to nivolumab or IC as first-line treatment for R/M SCCHN after progressing on or after platinum therapy (within 6 months) in the adjuvant or primary (i.e., with radiation) setting for locally advanced disease.

Abbreviations: CI, confidence interval; HPV, human papillomavirus; HR, hazard ratio; IC, investigator's choice; NE, not estimable; Nivo, nivolumab; OS, overall survival; R/M, recurrent or metastatic; SCCHN, squamous cell carcinoma of the head and neck.

Figure 2. OS in the overall intent-to-treat population.

Abbreviations: CI, confidence interval; HR, hazard ratio; IC, investigator's choice; Nivo, nivolumab; OS, overall survival.

Supplemental Figure 1. CONSORT diagram.

Abbreviations: R/M, recurrent or metastatic; SCCHN, squamous cell carcinoma of the head and neck.

Supplemental Figure 2. Treatment effect on overall survival by subgroup for the overall intent-to-treat population.

[a]Stratification factor.

Abbreviations: CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; HPV, human papillomavirus; HR, hazard ratio; IC, investigator's choice; Nivo, nivolumab.

FIGURES

Figure 1.

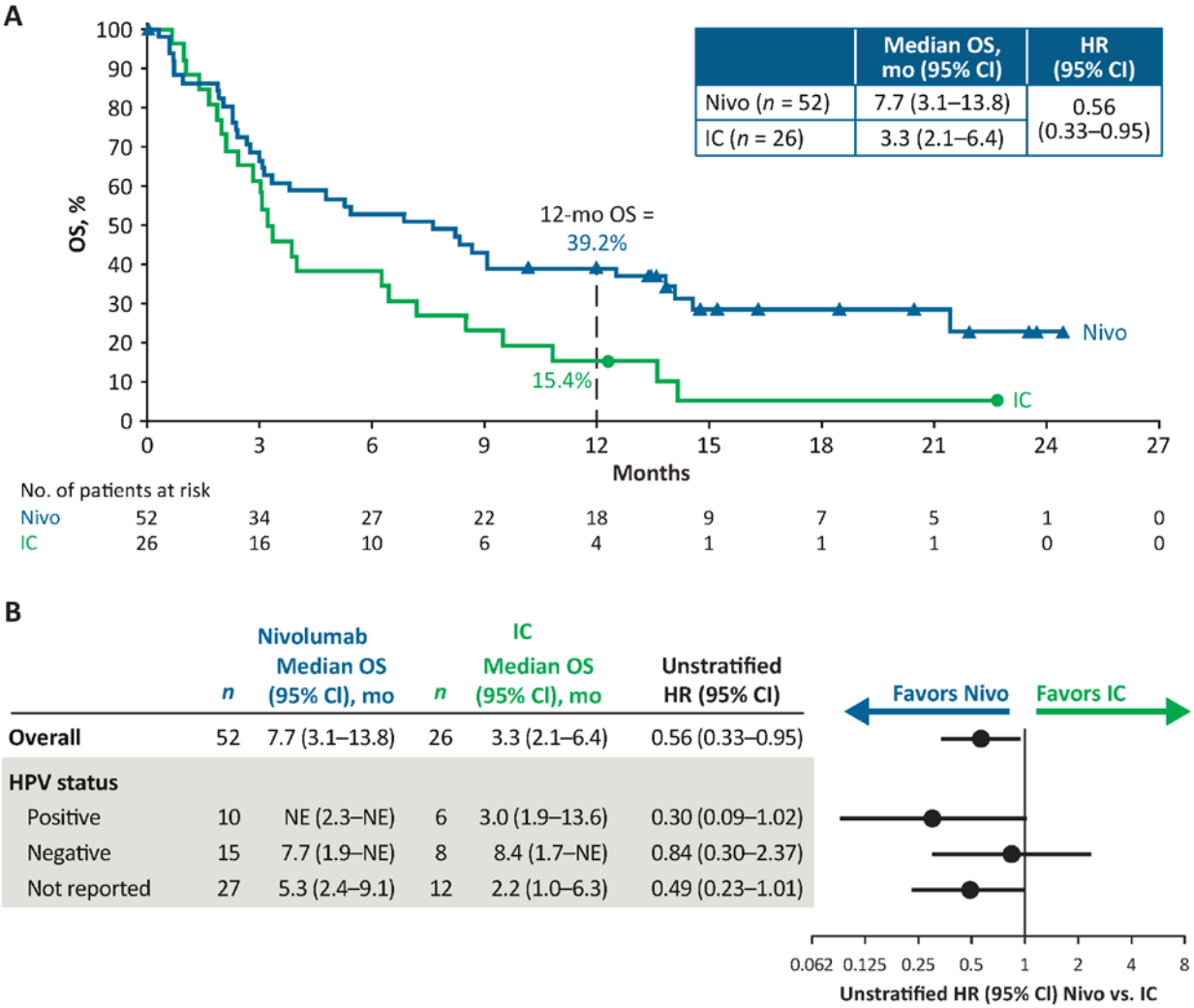
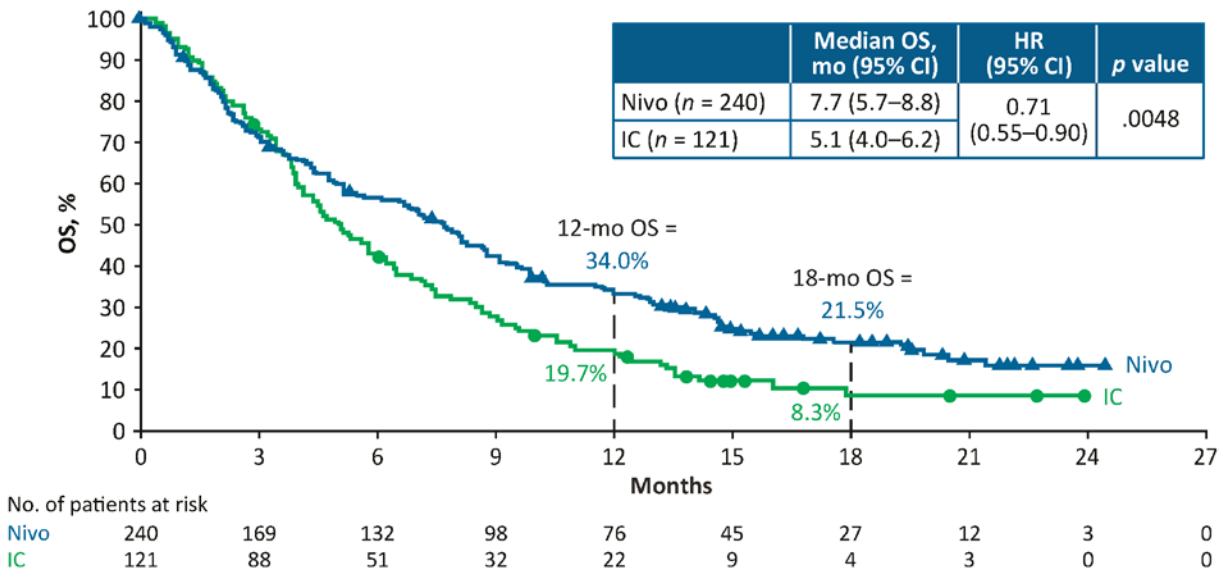


Figure 2.



SUPPLEMENTARY DATA

Supplemental Table 1. Baseline characteristics among patients randomized to nivolumab or investigator's choice as first-line treatment for recurrent or metastatic squamous cell carcinoma of the head and neck after progressing on or after platinum therapy (within 6 months) in the adjuvant or primary (i.e., with radiation) setting for locally advanced disease.

Characteristics	**Nivolumab (*n* = 52)**	**Investigator's choice (*n* = 26)**
Age, median (range), years	57.5 (30–79)	59.5 (28–78)
Age ⩾65 years, *n* (%)	13 (25.0)	9 (34.6)
Male, *n* (%)	41 (78.8)	21 (80.8)
Race, *n* (%)		
White	37 (71.2)	24 (92.3)
Black	4 (7.7)	1 (3.8)
Asian	9 (17.3)	1 (3.8)
Other	2 (3.8)	0
Region, *n* (%)		
North America	21 (40.4)	5 (19.2)
Europe	22 (42.3)	18 (69.2)
Rest of the world	9 (17.3)	3 (11.5)
Smoking or tobacco use, *n* (%)		
Current/former	40 (76.9)	17 (65.4)
Never	10 (19.2)	8 (30.8)
Unknown	2 (3.8)	1 (3.8)
ECOG performance status, *n* (%)		

Characteristics	Nivolumab (*n* = 52)	Investigator's choice (*n* = 26)
0	11 (21.2)	5 (19.2)
1	41 (78.8)	20 (76.9)
2	0	1 (3.8)
HPV status, *n* (%)		
Positive	10 (19.2)	6 (23.1)
Negative	15 (28.8)	8 (30.8)
Not tested[a]	27 (51.9)	12 (46.2)
PD-L1 expression, *n* (%)		
≥1%	24 (46.2)	14 (53.8)
<1%	13 (25.0)	7 (26.9)
Not quantifiable	15 (28.8)	5 (19.2)

[a]HPV status testing only required for patients with oropharyngeal cancer.

Abbreviations: ECOG, Eastern Cooperative Oncology Group; HPV, human papillomavirus; PD-L1, programmed death ligand 1.

Supplemental Table 2. Response among patients receiving nivolumab or investigator's choice as first-line treatment for recurrent or metastatic squamous cell carcinoma of the head and neck after progressing on or after platinum therapy (within 6 months) in the adjuvant or primary (i.e., with radiation) setting for locally advanced disease.

	Nivolumab (*n* = 52)	**Investigator's choice (*n* = 26)**
Best overall response, *n* (%)		
Complete response	2 (3.8)	0
Partial response	8 (15.4)	3 (11.5)
Stable disease	11 (21.2)	8 (30.8)
Progressive disease	18 (34.6)	8 (30.8)
Unable to determine	13 (25.0)	7 (26.9)
ORR, *n* (%)	10 (19.2)	3 (11.5)
[95% CI]	[9.6–32.5]	[1.2–10.4]
Odds ratio (95% CI)	1.83 (0.46–7.31)	
Time to response, median (range), months	2.0 (1.8–6.3)	2.0 (1.9–4.6)

Abbreviations: CI, confidence interval; ORR, objective response rate.

Supplemental Table 3. Most common TRAEs (≥10% in any arm) and select TRAEs among patients receiving nivolumab or investigator's choice as first-line treatment for recurrent or metastatic squamous cell carcinoma of the head and neck after progressing on or after platinum therapy (within 6 months) in the adjuvant or primary (i.e., with radiation) setting for locally advanced disease.

	Nivolumab (*n* = 51)		**Investigator's choice (*n* = 25)**	
Patients, *n* (%)	**Any grade**	**Grade 3–4**	**Any grade**	**Grade 3–4**
Any event (⩾10% in any arm)	35 (68.6)	14 (27.5)	18 (72.0)[a]	8 (32.0)
Fatigue	9 (17.6)	3 (5.9)	3 (12.0)	0
Nausea	7 (13.7)	0	5 (20.0)	0
Pruritus	6 (11.8)	0	0	0
Asthenia	4 (7.8)	0	5 (20.0)	1 (4.0)
Vomiting	3 (5.9)	0	3 (12.0)	0
Dry skin	2 (3.9)	0	3 (12.0)	0
Mucosal inflammation	1 (2.0)	0	5 (20.0)	0
Alopecia	0	0	4 (16.0)	0
Select TRAEs				
Skin	10 (19.6)	0	4 (16.0)	1 (4.0)
Endocrine	4 (7.8)	0	0	0
Gastrointestinal	4 (7.8)	1 (2.0)	2 (8.0)	0
Hepatic	3 (5.9)	0	1 (4.0)	0
Pulmonary	1 (2.0)	0	1 (4.0)	0
Renal	1 (2.0)	0	0	0
Hypersensitivity/infusion reactions	2 (3.9)	0	1 (4.0)	1 (4.0)

[a]Includes 1 grade 5 event of pneumonia.

Abbreviation: TRAE, treatment-related adverse event.

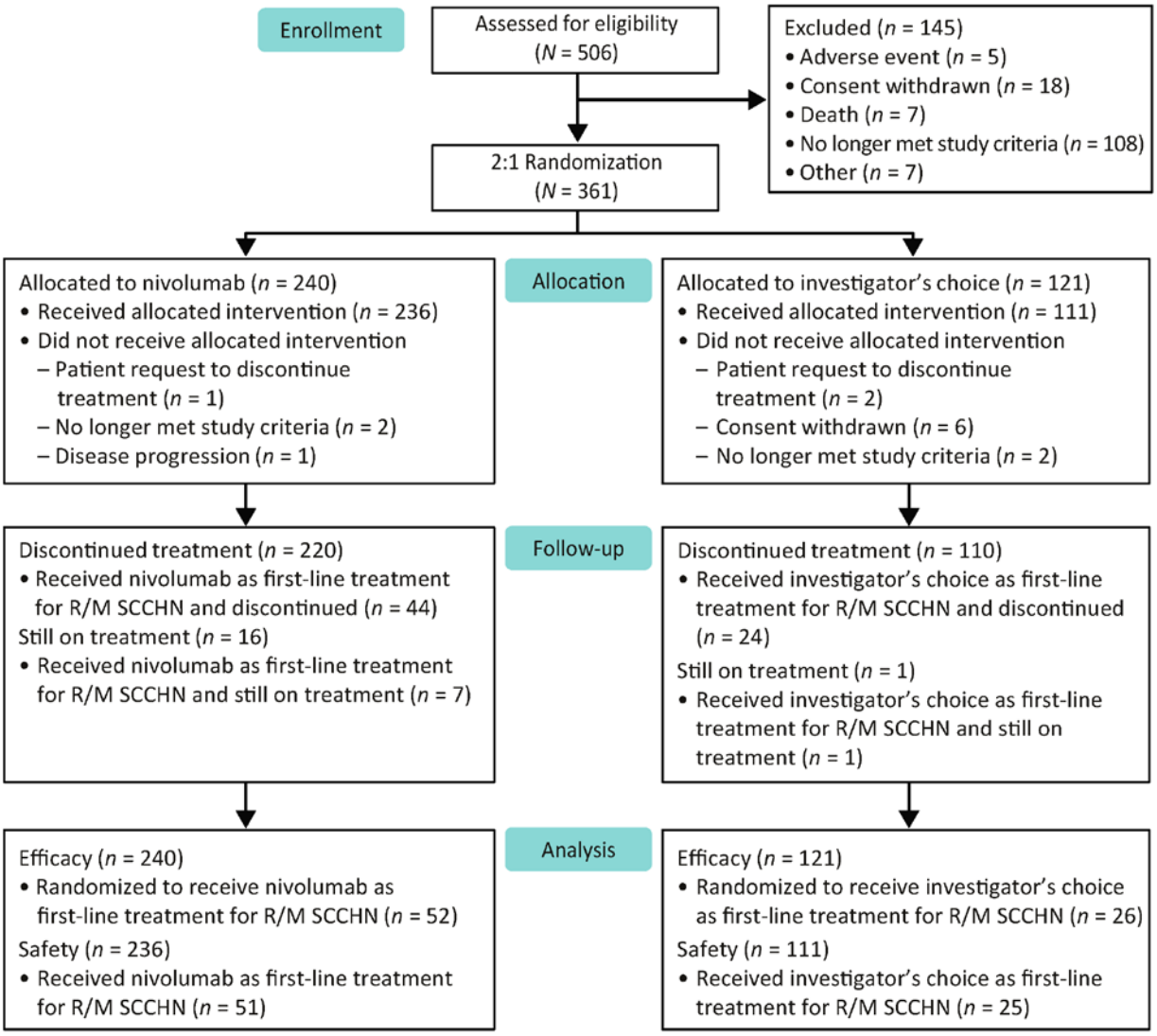
Supplemental Table 4. Most common TRAEs (≥10% in any arm) and select TRAEs in the overall treated population.

	Nivolumab (*n* = 236)		**Investigator's choice (*n* = 111)**	
Patients, *n* (%)	**Any grade**	**Grade 3–4**	**Any grade**	**Grade 3–4**
Any event (≥10% in any arm)	146 (61.9)	36 (15.3)	88 (79.3)[a]	40 (36.0)
Fatigue	37 (15.7)	5 (2.1)	20 (18.0)	3 (2.7)
Nausea	22 (9.3)	0	23 (20.7)	1 (0.9)
Diarrhea	20 (8.5)	1 (0.4)	16 (14.4)	2 (1.8)
Anemia	12 (5.1)	3 (1.3)	19 (17.1)	6 (5.4)
Asthenia	10 (4.2)	1 (0.4)	17 (15.3)	2 (1.8)
Stomatitis	6 (2.5)	1 (0.4)	12 (10.8)	3 (2.7)
Mucosal inflammation	4 (1.7)	0	15 (13.5)	2 (1.8)
Alopecia	0	0	14 (12.6)	0
Select TRAEs				
Skin	40 (16.9)	0	14 (12.6)	2 (1.8)
Endocrine	22 (9.3)	1 (0.4)	1 (0.9)	0
Gastrointestinal	20 (8.5)	1 (0.4)	17 (15.3)	2 (1.8)
Hepatic	7 (3.0)	2 (0.8)	5 (4.5)	1 (0.9)
Pulmonary	7 (3.0)	2 (0.8)	1 (0.9)	0
Renal	3 (1.3)	0	2 (1.8)	1 (0.9)
Hypersensitivity/infusion reactions	3 (1.3)	0	2 (1.8)	1 (0.9)

[a]Includes 1 grade 5 event of pneumonia.

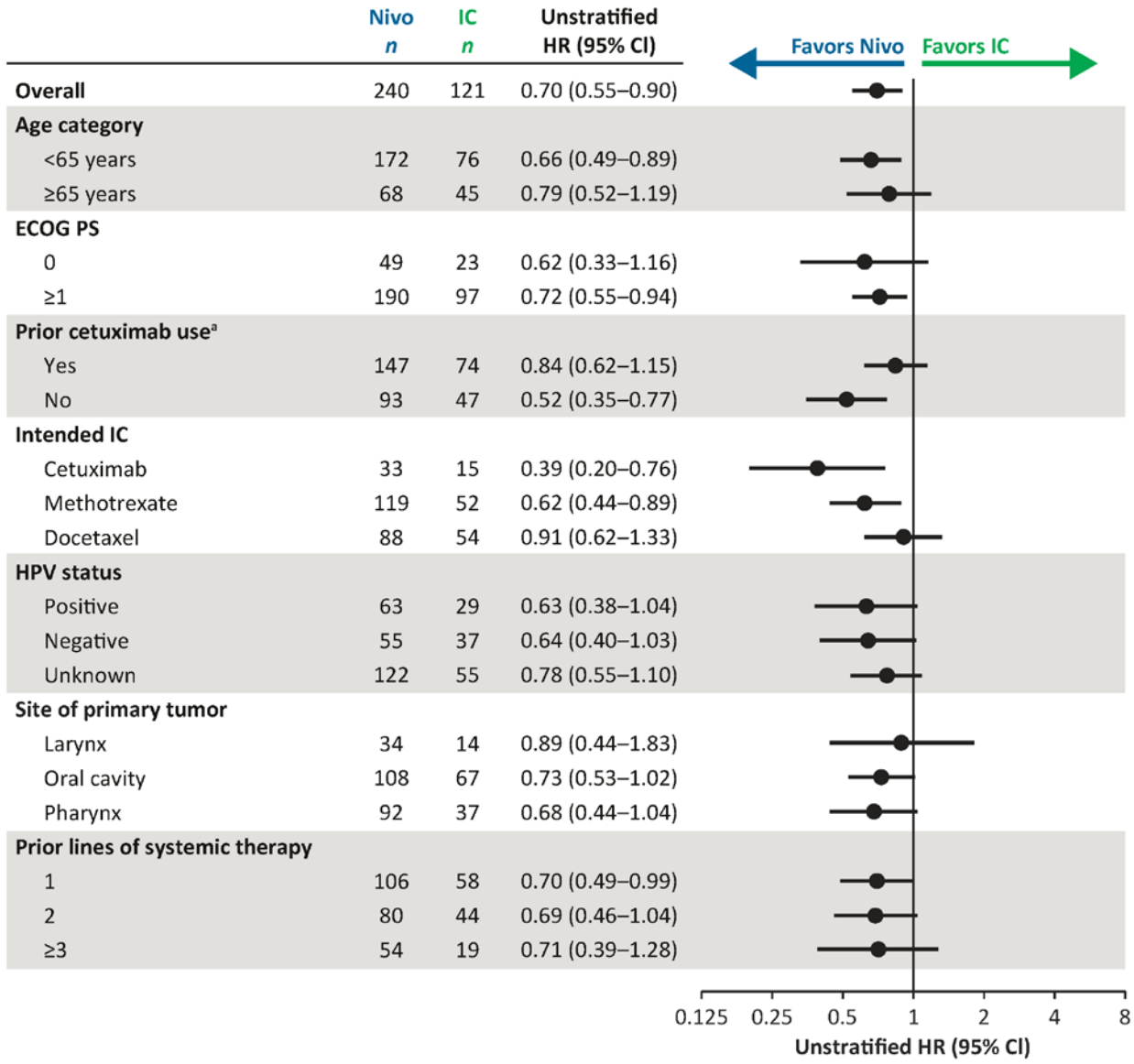
Abbreviation: TRAE, treatment-related adverse event.

Supplemental Figure 1. CONSORT diagram.



Abbreviations: R/M, recurrent or metastatic; SCCHN, squamous cell carcinoma of the head and neck.

Supplemental Figure 2. Treatment effect on overall survival by subgroup for the overall intent-to-treat population.



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