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

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Abstract (250/250)

Objectives: We report 2-year results from CheckMate 141 to establish the long-term efficacy and safety profile of nivolumab and outcomes by tumor PD-L1 expression in patients with recurrent or metastatic (R/M), platinum-refractory squamous cell carcinoma of the head and neck (SCCHN).

Methods: Patients with R/M SCCHN with tumor progression/recurrence within 6 months of platinum therapy were randomized 2:1 to nivolumab 3 mg/kg every 2 weeks or investigator's choice (IC). Primary endpoint: overall survival (OS). Data cutoff: September 2017.

Results: With 24.2 months' minimum follow-up, nivolumab (n = 240) continued to improve OS vs IC (n = 121), hazard ratio (HR) = 0.68 (95% CI 0.54–0.86). Nivolumab nearly tripled the estimated 24-month OS rate (16.9%) vs IC (6.0%), and demonstrated OS benefit across patients with tumor PD-L1 expression ≥1% (HR [95% CI] = 0.55 [0.39–0.78]) and <1% (HR [95% CI] = 0.73 [0.49–1.09]), and regardless of tumor HPV status. Estimated OS rates at 18, 24, and 30 months with nivolumab were consistent irrespective of PD-L1 expression (<1%/≥1%). In the nivolumab arm, there were no observed differences in baseline characteristics or safety profile between long-term survivors and the overall population. Grade 3–4 treatment-related adverse event rates were 15.3% and 36.9% for nivolumab and IC, respectively.

Conclusion: Nivolumab significantly improved OS at the primary analysis and demonstrated prolonged OS benefit vs IC and maintenance of a manageable and consistent safety profile with 2-year follow-up. OS benefit was observed with nivolumab irrespective of PD-L1 expression and HPV status. (Clinicaltrials.gov: NCT02105636)

Keywords (MeSH terms):

Nivolumab • Head and Neck Neoplasms • Carcinoma, squamous cell of head and neck • Immunotherapy • Papillomaviridae (Hpv, Human Papillomavirus Viruses) • Programmed Cell Death 1 Receptor • CD274 protein, human (PD-L1 Protein, Human) • Clinical Trial, Phase III • Survival Analysis • Survivors (Long-term Survivors)

Highlights:

- Nivolumab showed prolonged OS benefit in patients with R/M SCCHN post-platinum
- Long-term OS benefit was observed irrespective of PD-L1 expression or HPV status
- No new safety concerns were identified from long-term nivolumab treatment

Introduction

Squamous cell carcinoma of the head and neck (SCCHN) includes neoplasms in the oral cavity, pharynx, and larynx, and accounts for 90% of all head and neck cancers [1-3]. Patients with recurrent/metastatic (R/M) SCCHN who progress within 6 months after platinum-based therapy have poor long-term prognosis and limited treatment options, with a median overall survival (OS) of ≤6 months [4, 5].

CheckMate 141 evaluated the efficacy, safety, and patient-reported quality of life of nivolumab monotherapy vs standard single agent of investigator's choice (IC) in patients with R/M SCCHN who experienced tumor progression or recurrence within 6 months of platinum-based therapy administered in the adjuvant, primary (ie, with radiation), recurrent, or metastatic setting [6, 7]. Nivolumab is the only immunotherapy to significantly improve OS at the primary analysis in this patient population, hazard ratio (HR) vs IC = 0.70 (97.73% confidence interval [CI] 0.51–0.96); p = 0.01 [6]. With 1-year follow-up, nivolumab continued to improve OS compared with IC; HR = 0.71 (95% confidence interval [CI]: 0.55, 0.90) [8]. The Kaplan-Meier–estimated 18-month OS rate with nivolumab was nearly triple that with IC (21.5% vs 8.3%). The objective response rate (ORR) with nivolumab was more than twice that of IC (13.3% vs 5.8%). The safety profile of nivolumab was manageable, with fewer grade 3–4 treatment-related adverse events (TRAEs) compared with IC. Nivolumab also stabilized quality-of-life measures, whereas clinically meaningful deterioration was observed with IC [7]. Here, we report long-term (2-year) follow-up of CheckMate 141 in the overall population, as well as in subgroups defined by baseline tumor programmed death ligand 1 (PD-L1) expression and human papillomavirus (HPV) status.

Patients and methods

Study design and patients

CheckMate 141 is a randomized, open-label, phase 3 trial (NCT02105636), the detailed study design of which has been described previously [6]. Briefly, eligible patients were 18 years of age or older, had histologically confirmed R/M SCCHN of the oral cavity, oropharynx, hypopharynx, or larynx, and had tumor progression on or within 6 months after the last dose of platinum-based chemotherapy administered in the locally advanced, recurrent, or metastatic disease setting. Patients were randomized 2:1, stratified by prior cetuximab treatment, to receive nivolumab (3 mg/kg every 2 weeks) or standard single agent of IC (methotrexate 40–60 mg/m^2 weekly, docetaxel 30–40 mg/m^2 weekly, or cetuximab 400 mg/m^2 once, then 250 mg/m^2 weekly). Treatment continued until tumor progression or unacceptable toxicity. Patients in the nivolumab arm were allowed to continue nivolumab treatment beyond tumor progression if they met predefined, protocol-specified criteria [9].

CheckMate 141 was conducted in accordance with the ethical principles in the Declaration of Helsinki. All patients provided written informed consent prior to enrollment. The study was approved by the institutional review board or independent ethics committee at each center and was conducted in accordance with Good Clinical Practice guidelines defined by the International Conference on Harmonisation.

Outcomes

The primary endpoint was OS, defined as the time from randomization to death due to any cause. Secondary endpoints included progression-free survival (PFS) and ORR. Tumor responses were evaluated every 6 weeks from week 9 until progression or treatment discontinuation using Response Evaluation Criteria In Solid Tumors (RECIST) v1.1 [10]. Safety was evaluated using the Common Terminology Criteria for Adverse Events, version 4.0. Adverse events with potential immunologic cause were classified as select adverse events.

Exploratory biomarker analyses

Fresh or archival pretreatment tumor specimens were obtained after the last therapy and prior to trial entry. Tumor PD-L1 membrane expression was evaluated centrally by immunohistochemical testing using the Dako PD-L1 IHC 28-8 pharmDx assay in a minimum of 100 evaluable tumor cells. Patients were defined as PD-L1 expressors if their tumor had ≥1% PD-L1 expression and non-expressors if their tumor had <1% PD-L1 expression. Documented tumor HPV status, assessed by p16 immunohistochemical testing by local or central analysis, was required for patients with oropharyngeal cancer. Tumors were defined as HPV positive if diffuse staining was present in at least 70% of tumor cells.

Statistical analyses

The current analyses are based on a September 2017 data cutoff, representing a minimum follow-up of 24.2 months. Efficacy analyses were conducted in all randomized patients (intent-to-treat [ITT] population), and safety analyses were conducted in all treated patients.

OS and PFS were assessed using the Kaplan-Meier method, and HRs and corresponding 2-sided 95% CIs were estimated using a Cox proportional hazards model. A generalization of the Brookmeyer and Crowley method was used to compute CIs for median survival times, and a 2-sided Cochran-Mantel-Haenszel test was used to compute the odds ratio and associated CIs for tumor response.

Results

Patients

Baseline characteristics of the 361 randomized patients have been described previously [6]. Compared with the original analysis [6], baseline tumor PD-L1 expression and HPV status were quantifiable in 15 and 8 additional patients, respectively (Table 1). At the time of this analysis, 8 (3.4%) patients remained on treatment in the nivolumab arm compared with 0 in the IC arm (Supplementary Table 1 and Supplementary Fig. 1). Sixteen patients in the nivolumab arm discontinued treatment between 1 and 2 years, most commonly due to disease progression (n = 8); 2 patients discontinued nivolumab therapy after 2 years (1 each due to adverse events unrelated to study drug and patient request). No patient discontinued nivolumab therapy after 2 years due to disease progression or treatment-related toxicity. The median (range) duration of treatment was 1.9 (0 to 36+) months for nivolumab and 1.9 (0 to 13) months for IC. After treatment discontinuation, 5.3% of patients in the nivolumab arm and 10.1% of patients in the IC arm received subsequent immunotherapy (nivolumab, pembrolizumab, durvalumab, or urelumab) (Supplementary Table 2).

Efficacy in overall study population

Consistent with the primary analysis, nivolumab demonstrated sustained OS benefit compared with IC, with a 32% reduction in risk of death; HR = 0.68 (95% CI 0.54–0.86) with long-term follow-up (minimum 24.2 months). Median (95% CI) OS was 7.7 (5.7–8.8) months in the nivolumab arm and 5.1 (4.0–6.2) months in the IC arm (Fig. 1). The Kaplan-Meier–estimated 24-month OS rate with nivolumab (16.9% [95% CI 12.4%–22.0%]) was nearly triple that of IC (6.0% [95% CI 2.7%–11.3%]). The estimates of the HR for death among prespecified demographic and clinical subgroups, including age, Eastern Cooperative Oncology Group (ECOG) performance status, tumor site, and prior lines of systemic therapy, were generally

consistent with the ITT population, favoring nivolumab (Supplementary Fig. 2). With longer follow-up, PFS (HR = 0.87 [95% CI 0.68–1.11]) was similar to previous analyses [6, 8].

The ORR was unchanged from previous analyses (Table 2) [6, 8]. In the nivolumab arm, 7 complete responses were observed, including 1 patient who had a partial response at the previous analysis, but since then converted to a complete response. The median (range) time to response remained unchanged in both treatment arms from previous follow-ups, 2.1 (1.8 to 7.4) months for nivolumab vs 2.0 (1.9 to 4.6) months for IC [6]. The median (range) duration of response with nivolumab treatment was more than double that with IC (9.7 [2.8 to 32.8+] vs 4.0 [1.5+ to 11.3]).

Tumor PD-L1 expression and HPV status

OS benefit with nivolumab vs IC was demonstrated across PD-L1 expressors and non-expressors (Fig. 2). With long-term follow-up, nivolumab continued to provide OS benefit in PD-L1 expressors, with a consistent 45% reduction in the risk of death compared with IC (HR = 0.55 [95% CI 0.39–0.78]) (Fig. 2A). In PD-L1 non-expressors, nivolumab demonstrated a 27% reduction in the risk of death compared with IC (HR = 0.73 [95% CI 0.49–1.09] (Fig. 2B). For these patients, HR (95% CI) trended lower as follow-up time increased: 0.83 (0.54–1.29) and 0.89 (0.54–1.45) at the 1-year (September 2016 data cutoff, Supplementary Fig 3A) and primary analysis (December 2015 data cutoff, Supplementary Fig. 3B) [6], respectively. Kaplan-Meier estimated OS rates with nivolumab were consistent between PD-L1 expressors and non-expressors at 18 (24.0% and 26.2%, respectively), 24 (18.5% and 20.7%), and 30 (13.7% and 11.2%) months (Fig. 2). Median PFS for nivolumab was similar across PD-L1 subgroups and was not differentiated from IC in either subgroup, 2.1 (95% CI 2.0–3.4) months and 2.0 (95% CI 1.9–2.1) months in PD-L1 expressors and non-expressors, respectively, in the nivolumab arm, and 2.0 (95% CI 1.9–3.1) months and 2.7 (95% CI 2.0–4.6) months in PD-L1 expressors and

non-expressors in the IC arm. The HR for PFS was 0.59 (95% CI 0.41–0.84) in PD-L1 expressors and 1.13 (95% CI 0.75–1.71) in PD-L1 non-expressors. Nivolumab improved ORR compared with IC in PD-L1 expressors; ORR was similar across treatment arms in PD-L1 non-expressors (Supplementary Table 3). Complete responses were observed across PD-L1 expressors (n = 2), non-expressors (n = 2), and PD-L1 non-quantifiable (n = 3).

OS benefit with nivolumab was observed in both patients with HPV-positive and HPV-negative tumors, and benefit was maintained with long-term (2-year) follow-up (Fig. 3). Nivolumab demonstrated approximately 40% reduction in the risk of death compared with IC in both the HPV-positive subgroup (HR = 0.60 [95% CI 0.37–0.97]) as well as the HPV-negative subgroup (HR = 0.59 [95% CI 0.38–0.92]). Nivolumab improved ORR compared with IC in patients with HPV-positive tumors; ORR was similar across treatment arms in patients with HPV-negative tumors (Supplementary Table 3).

Overall survival was further analyzed in subgroups defined according to both tumor HPV status and PD-L1 expression (Supplementary Fig. 4). Nivolumab prolonged median OS vs IC in each of the 4 subgroups, with the greatest benefit (HR = 0.39 [95% CI 0.18–0.81]) found among PD-L1 expressors with HPV-positive tumors. The results of this analysis should be interpreted with caution, as sample sizes and power were limited.

Safety

Among all treated patients (n = 347), nivolumab demonstrated a favorable safety profile compared with IC with long-term follow-up. The safety profile remained manageable and consistent with previous analyses [6, 8], with fewer grade 3–4 TRAEs in the nivolumab arm compared with the IC arm (Table 3). Most grade 3–4 TRAEs occurred within the first 6 months of initiating treatment; 19.5%, 2.5%, and 1.7% of patients in the nivolumab arm experienced grade 3–4 TRAEs within the first 6 months, between 6 and 12 months, and at or after 12 months

of initiating study treatment, respectively. There were 6 patients with grade 3 TRAEs first occurring after 12 months of initiating therapy; 4 in the nivolumab arm (hyperlipasemia and hyperamylasemia; hyponatremia; deterioration of diabetes mellitus; and lipase increased and weight decreased), and 2 patients in the IC arm (hypothyroidism and increased aspartate aminotransferase); no patients experienced grade 4 TRAEs during this time frame. The most common select TRAEs in the nivolumab and IC arms were skin-related and gastrointestinal, respectively (Table 3). The incidence of serious TRAEs was lower in the nivolumab arm (7.2%) compared with the IC arm (15.3%). A greater proportion of patients in the IC arm compared with the nivolumab arm discontinued the study due to TRAEs at any time (9.0% vs 4.2%). Four TRAEs led to discontinuation between 1 and 2 years in the nivolumab arm: nephritis; pneumonitis; uncontrollable diabetes mellitus, chronic heart failure, and fatigue; and lipase elevation with progressive weight loss (n = 1 each). The number of treatment-related deaths remained unchanged from the primary analysis [6], (2 deaths in the nivolumab arm [1 each due to pneumonitis and hypercalcemia], and 1 death in the IC arm due to treatment-related lung infection).

Post hoc analysis of 2-year survivors

In the nivolumab arm, 37 patients (15.4%) were alive (in survival follow-up) at 2 years. There were no observed differences in baseline demographic or disease characteristics among patients in the nivolumab arm who were alive at 2 years compared with the nivolumab ITT population (Table 4). The safety profile of 2-year survivors in the nivolumab arm was consistent with all nivolumab-treated patients (Supplementary Table 4); however, a relatively higher rate of any-grade TRAEs was reported in 2-year survivors (89.2%) vs in all nivolumab-treated patients (61.9%). Fatigue was the most common TRAE among all nivolumab-treated patients and 2-year survivors. Disease progression was the most frequent primary cause of death in both study

arms, both among patients who experienced late death (>24 months after the first dose) and those who experienced early death.

DISCUSSION

With long-term (minimum 2-year) follow-up, nivolumab demonstrated prolonged OS benefit compared with IC and maintained a favorable safety profile in patients with R/M SCCHN post–platinum therapy. At the time of the current analysis, there were 8 patients (3.4%) continuing on nivolumab treatment and no patients continuing on IC.

Nivolumab is the only immunotherapy to demonstrate OS benefit across PD-L1 expressors/non-expressors in this patient population. Notably, Kaplan-Meier–estimated OS rates at 18, 24, and 30 months among nivolumab patients were consistent between PD-L1 expressors and non-expressors. Among PD-L1 expressors, OS benefit vs IC was observed at the primary analysis [6] and maintained at the 2-year follow-up. Among PD-L1 non-expressors, the HR for death consistently trended lower as follow-up time increased, suggesting a long-term benefit of nivolumab in this patient population. An assessment of the patients who had tumor PD-L1 data at the time of the primary analysis (excluding additional patients with quantifiable PD-L1 expression since the primary analysis) resulted in a HR of 0.77 (95% CI 0.51–1.15). In addition to the OS benefit seen, complete responses were observed across PD-L1 expressors/non-expressors.

Both patients with HPV-positive and HPV-negative tumors benefited from nivolumab therapy, and this was maintained with long-term follow-up. Notably, with current follow-up, Kaplan-Meier OS curves were similar between both HPV subgroups, and the HRs were nearly identical. Given the worse prognosis historically seen among patients with HPV-negative SCCHN [11], nivolumab helps address the unmet medical need in this population.

The median duration of response in the current analysis for each arm was similar to that of 1 year; however, the upper limit of the range for nivolumab arm continued to increase, further

suggesting that patients who remained on nivolumab continued to experience long-term benefit. Importantly, the OS benefit was seen despite ~10% of patients in the IC arm receiving subsequent immunotherapy, reinforcing the significance of the OS results.

There were no observed differences in baseline characteristics, including tumor PD-L1 expression and HPV status, among nivolumab-treated patients who were alive at 2 years compared with the nivolumab ITT population. Similarly, the safety profile of patients alive at 2 years in the nivolumab arm was consistent with all nivolumab-treated patients; this lack of new safety signals with long-term follow-up suggests a predictable safety profile. The slightly higher rate of any-grade TRAEs among 2-year survivors compared with all treated patients was likely due to these patients having longer follow-up, and thus having more time to experience TRAEs.

In CheckMate 141, nivolumab was dosed according to a weight-based regimen (3 mg/kg every 2 weeks), which was also the initial approved regimen in the United States and other countries. Recently, however, a flat dose of 240 mg every 2 weeks or 480 mg every 4 weeks via 30-minute intravenous infusion was approved in the United States [12]. The 240 mg every 2 week dosing regimen was also recently recommended by the Committee for Medicinal Products for Human Use of the European Medicines Agency [13]. This added flexibility in dosing could decrease the burden of healthcare visits for patients and caregivers.

Conclusion

Nivolumab is an established therapeutic option in R/M SCCHN post-platinum therapy and the only immunotherapy to demonstrate significant OS improvement in the primary analysis of a phase 3 study (CheckMate 141). Nivolumab is also the only immunotherapy to stabilize QoL in this patient population. With long-term follow-up, nivolumab demonstrated prolonged OS benefit compared with IC (methotrexate, docetaxel, or cetuximab) and maintained a favorable safety

profile, with no new safety signals identified. Nivolumab demonstrated OS benefit across PD-L1 expressors/non-expressors and irrespective of HPV status in this patient population

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TABLES

Table 1

Baseline tumor PD-L1 expression and HPV status.

Patients, n (%)	Nivolumab (n = 240)	IC (n = 121)
Tumor PD-L1 expression		
Non-expressors (<1%)	76 (31.7)	40 (33.1)
Expressors (≥1%)	96 (40.0)	63 (52.1)
Not quantifiable	68 (28.3)	18 (14.9)
Tumor HPV status		
Positive	64 (26.7)	29 (24.0)
Negative	56 (23.3)	37 (30.6)
Unknown/not reported	120 (50.0)	55 (45.5)

IC, investigator's choice; HPV, human papillomavirus; PD-L1, programmed death ligand 1.

Table 2

Best overall response.

	Nivolumab (n = 240)	IC (n = 121)
Best overall response, n (%)		
Complete response	7 (2.9)	1 (0.8)
Partial response	25 (10.4)	6 (5.0)
Stable disease	55 (22.9)	43 (35.5)
Progressive disease	99 (41.3)	42 (34.7)
Unable to determine	54 (22.5)	29 (24.0)
ORR, % (95% CI)	13.3 (9.3–18.3)	5.8 (2.4–11.6)
Time to response, median (range), mo	2.1 (1.8–7.4)	2.0 (1.9–4.6)
Duration of response, median (range), mo	9.7 (2.8 to 32.8+)	4.0 (1.5+ to 11.3)

CI, confidence interval; IC, investigator's choice; ORR, objective response rate.

Table 3

Most common TRAEs (≥15% in any arm) and select TRAEs among all treated patients.

Patients, n (%)	Nivolumab (n = 236)		IC (n = 111)	
	Any grade	Grade 3–4	Any grade	Grade 3–4
Any TRAE	146 (61.9)	36 (15.3)	88 (79.3)	41 (36.9)
TRAEs in ≥15% of patients				
Fatigue	37 (15.7)	5 (2.1)	20 (18.0)	3 (2.7)
Nausea	22 (9.3)	0	23 (20.7)	1 (0.9)
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)
Select TRAEs				
Skin	41 (17.4)	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)	16 (14.4)	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
Hypersensitivity/infusion reactions	3 (1.3)	0	2 (1.8)	1 (0.9)
Renal	3 (1.3)	0	2 (1.8)	1 (0.9)

IC, investigator's choice; TRAEs, treatment-related adverse events.

Table 4

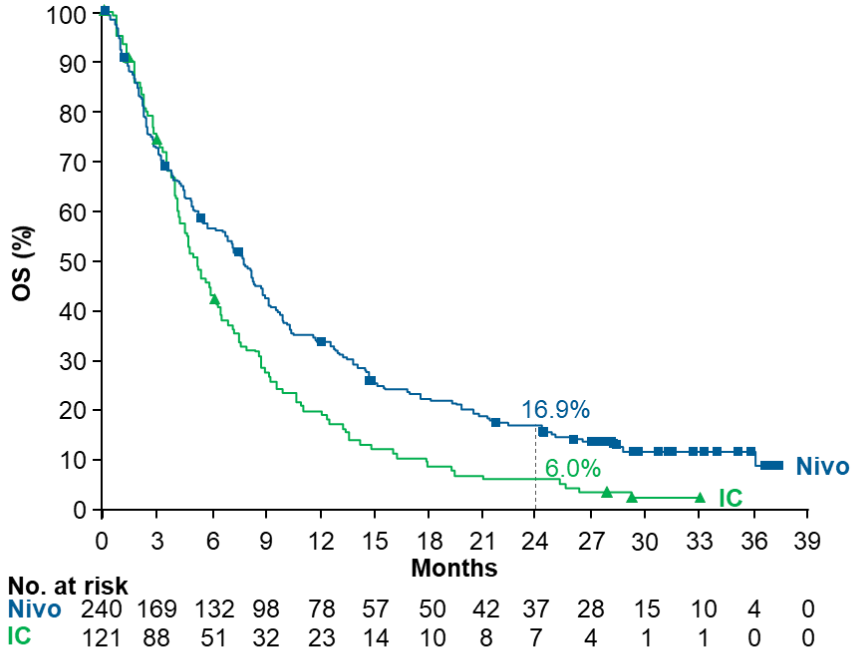
Baseline characteristics in the nivolumab arm among the ITT population and 2-year survivors.

	Nivolumab	
Patients, n (%)	ITT (n = 240)	2-year survivors (n = 37)
ECOG performance status		
0	49 (20.4)	10 (27.0)
≥1	190 (79.2)	27 (73.0)
Not reported	1 (0.4)	0
Tobacco use		
Current/former	191 (79.6)	31 (83.8)
Never	39 (16.3)	6 (16.2)
Unknown	10 (4.2)	0
Prior cetuximab use		
Yes	147 (61.3)	19 (51.4)
No	93 (38.8)	18 (48.6)
Number of lines of prior systemic therapy		
1	106 (44.2)	14 (37.8)
2	80 (33.3)	16 (43.2)
≥3	54 (22.5)	7 (18.9)
Site of primary tumor		
Oral cavity	108 (45.0)	13 (35.1)
Pharynx	92 (38.3)	17 (45.9)
Larynx	34 (14.2)	5 (13.5)
Other	6 (2.5)	2 (5.4)
Tumor PD-L1 expression		
Expressors (≥1%)	96 (40.0)	16 (43.2)
Non-expressors (<1%)	76 (31.7)	15 (40.5)
Tumor HPV status		
Positive	64 (26.7)	12 (32.4)
Negative	56 (23.3)	13 (35.1)
Unknown/not reported	120 (50.0)	12 (32.4)

ECOG, Eastern Cooperative Oncology Group; HPV, human papillomavirus; ITT, intent-to-treat; PD-L1, programmed death ligand 1.

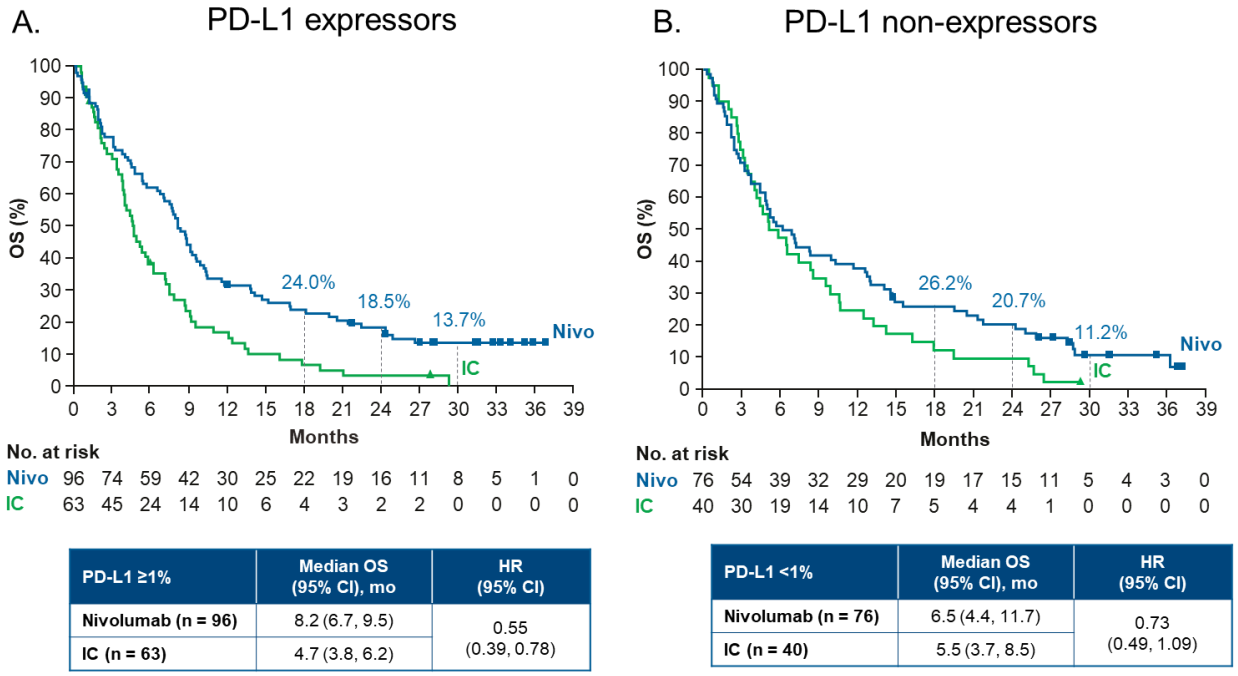
FIGURES

Fig. 1. Overall survival (OS) with a minimum follow-up of 24.2 months (intent-to-treat population). Symbols represent censored observations; dotted lines indicate OS rate time points. CI, confidence interval; HR, hazard ratio; IC, investigator's choice; Nivo, nivolumab.



	Median OS (95% CI), mo	HR (95% CI)
Nivolumab (n = 240)	7.7 (5.7, 8.8)	0.68 (0.54, 0.86)
IC (n = 121)	5.1 (4.0, 6.2)	

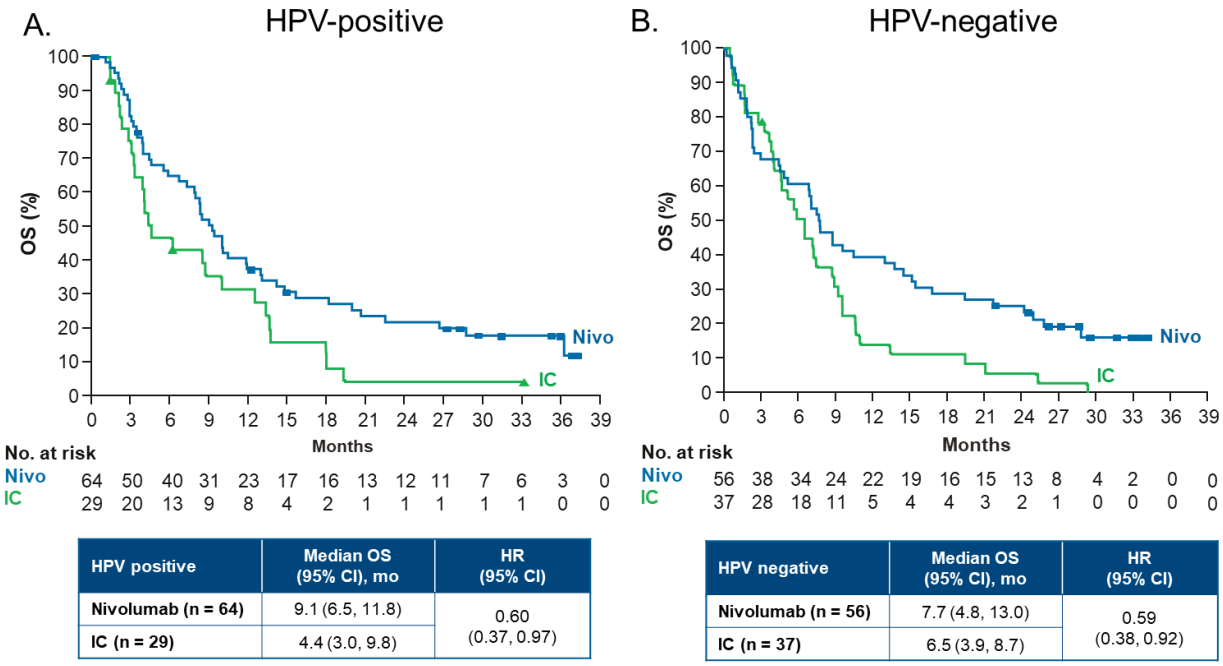
Fig. 2. Overall survival (OS) in programmed death ligand 1 (PD-L1) expressors (A) and PD-L1 non-expressors (B). Symbols represent censored observations. CI, confidence interval; HR, hazard ratio; IC, investigator's choice; Nivo, nivolumab.



PD-L1 ≥1%	Median OS (95% CI), mo	HR (95% CI)
Nivolumab (n = 96)	8.2 (6.7, 9.5)	0.55 (0.39, 0.78)
IC (n = 63)	4.7 (3.8, 6.2)	

PD-L1 <1%	Median OS (95% CI), mo	HR (95% CI)
Nivolumab (n = 76)	6.5 (4.4, 11.7)	0.73 (0.49, 1.09)
IC (n = 40)	5.5 (3.7, 8.5)	

Fig. 3. Overall survival (OS) by tumor human papillomavirus (HPV) status, positive (A) and negative (B). Symbols represent censored observations. CI, confidence interval; HR, hazard ratio; IC, investigator's choice; Nivo, nivolumab.



HPV positive	Median OS (95% CI), mo	HR (95% CI)
Nivolumab (n = 64)	9.1 (6.5, 11.8)	0.60 (0.37, 0.97)
IC (n = 29)	4.4 (3.0, 9.8)	

HPV negative	Median OS (95% CI), mo	HR (95% CI)
Nivolumab (n = 56)	7.7 (4.8, 13.0)	0.59 (0.38, 0.92)
IC (n = 37)	6.5 (3.9, 8.7)	

Supplementary Table 1
Patient disposition.

Patients, n (%)	Nivolumab (n = 236)	IC (n = 111)
Continuing treatment	8 (3.4)	0
Not continuing treatment	228 (96.6)	111 (100.0)
Disease progression	182 (77.1)	87 (78.4)
AE unrelated to study drug	19 (8.1)	3 (2.7)
Study drug toxicity	12 (5.1)	10 (9.0)
Patient request to discontinue/withdrawal of consent	12 (5.1)	7 (6.3)
Other[a]	3 (1.3)	4 (3.6)

[a] Other includes loss to follow-up, poor/noncompliance, maximum clinical benefit, and patient no longer meeting study criteria.
AE, adverse event; IC, investigator's choice.

Supplementary Table 2.
Subsequent therapies.

Patients, n (%)	Nivolumab (n = 228)	IC (n = 109)
Any subsequent therapy[a]	91 (39.9)	43 (39.4)
Radiotherapy	30 (13.2)	14 (12.8)
Surgery	2 (0.9)	3 (2.8)
Systemic therapy	82 (36.0)	36 (33.0)
Monoclonal antibody[b]	31 (13.6)	8 (7.3)
Taxane	35 (15.4)	11 (10.1)
Other – approved agent	31 (13.6)	12 (11.0)
Folic acid analog	22 (9.6)	7 (6.4)
Platinum-based chemotherapy	16 (7.0)	11 (10.1)
Other – experimental agent	15 (6.6)	3 (2.8)
Immunotherapy[c]	12 (5.3)	11 (10.1)
PD-1/PD-L1 inhibitors	9 (3.9)	10 (9.2)
Unassigned	1 (0.4)	0

[a] Patients may have received more than 1 type of subsequent therapy, which was defined as non-study anti-cancer therapy started on or after first dosing date (or randomization date, if patient was not treated).
[b] Bevacizumab, cetuximab.
[c] Nivolumab, pembrolizumab, durvalumab, urelumab.
IC, investigator's choice; PD-1, programmed death 1; PD-L1 programmed death ligand 1.

Supplementary Table 3

Best overall response by tumor PD-L1 expression and HPV status.

ORR, % (95% CI)	Nivolumab	IC
PD-L1 expressors	17.7 (10.7–26.8) [n = 96]	1.6 (0.04–8.5) [n = 63]
PD-L1 non-expressors	11.8 (5.6–21.3) [n = 76]	12.5 (4.2–26.8) [n = 40]
HPV-positive	17.2 (8.9–28.7) [n = 64]	3.4 (0.1–17.8) [n = 29]
HPV-negative	14.3 (6.4–26.2) [n = 56]	10.8 (3.0–25.4) [n = 37]

CI, confidence interval; HPV, human papillomavirus; IC, investigator's choice; ORR, objective response rate; PD-L1, programmed death ligand 1.

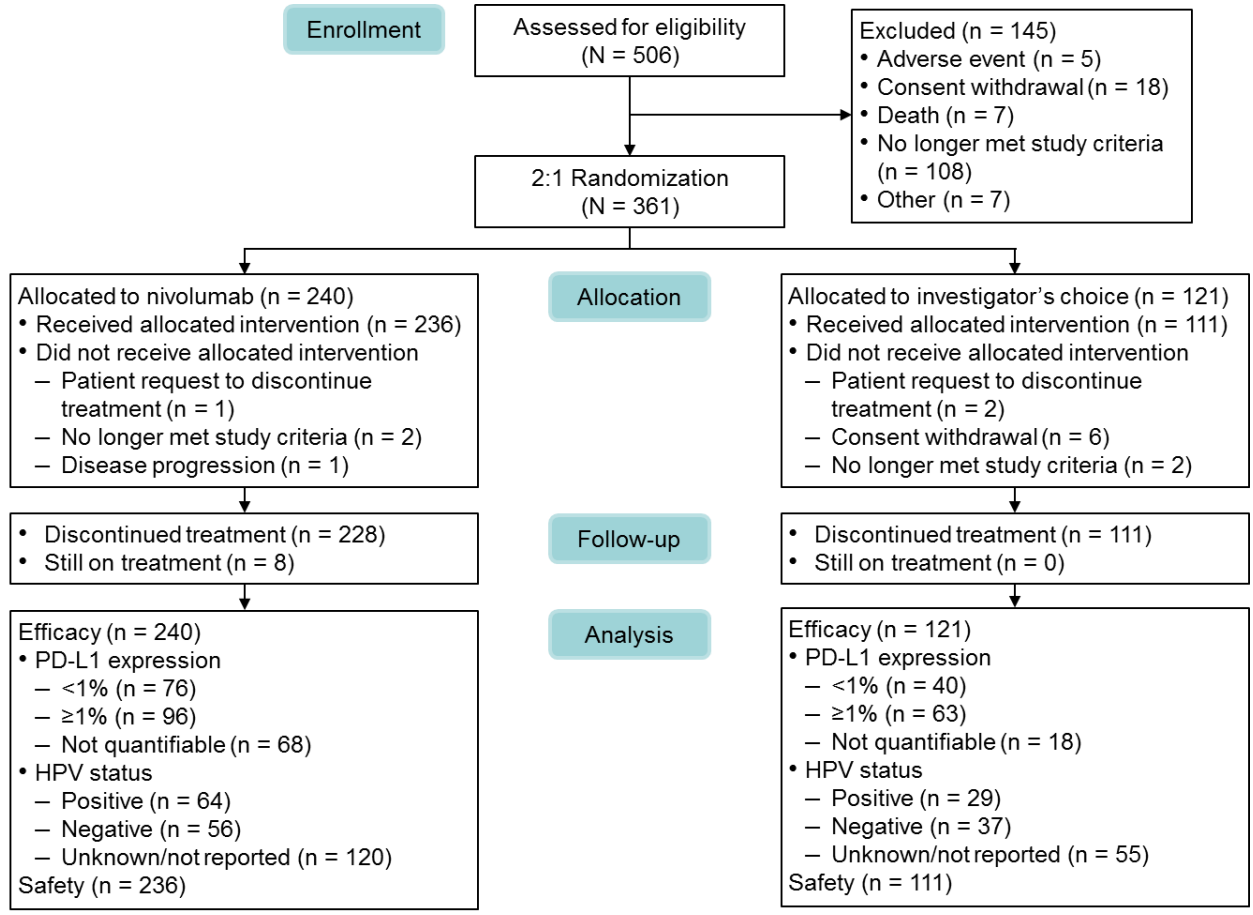
Supplementary Table 4

TRAEs in ≥10% of all nivolumab-treated patients or nivolumab 2-year survivors.

	Nivolumab			
	All treated (n = 236)		2-year survivors (n = 37)	
Patients	Any grade	Grade 3–4	Any grade	Grade 3–4
Any TRAE, n (%)	146 (61.9)	36 (15.3)	33 (89.2)	10 (27.0)
Fatigue	37 (15.7)	5 (2.1)	10 (27.0)	1 (2.7)
Nausea	22 (9.3)	0	7 (18.9)	0
Diarrhea	20 (8.5)	1 (0.4)	5 (13.5)	0
Pruritus	19 (8.1)	0	6 (16.2)	0
Rash	19 (8.1)	0	8 (21.6)	0
Decreased appetite	19 (8.1)	0	5 (13.5)	0
Hypothyroidism	14 (5.9)	0	4 (10.8)	0
Asthenia	10 (4.2)	1 (0.4)	4 (10.8)	0
Lipase increased	9 (3.8)	6 (2.5)	4 (10.8)	3 (8.1)
Amylase increased	8 (3.4)	3 (1.3)	4 (10.8)	2 (5.4)
Cough	7 (3.0)	1 (0.4)	4 (10.8)	0
Hypertension	6 (2.5)	1 (0.4)	4 (10.8)	1 (2.7)

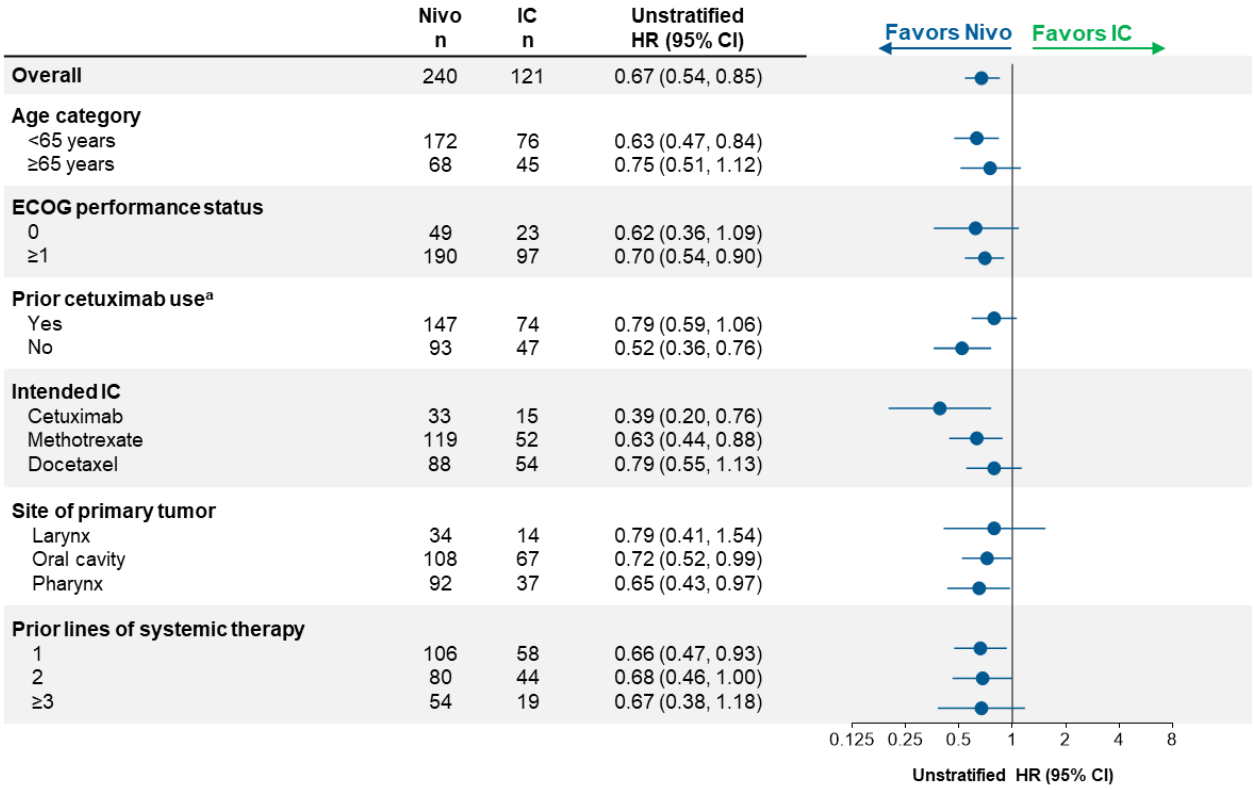
TRAEs, treatment-related adverse events.

Supplementary Fig. 1. CONSORT diagram (minimum follow-up, 24.2 months).



HPV, human papillomavirus; PD-L1, programmed death ligand 1.

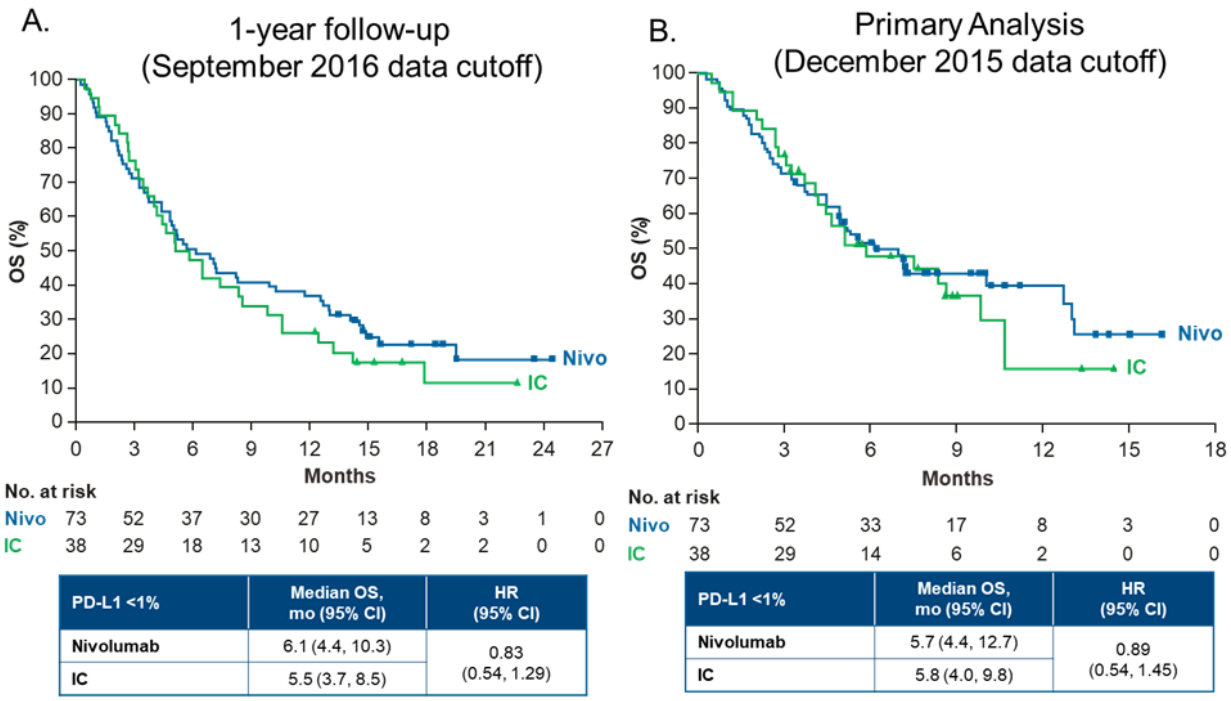
Supplementary Fig. 2. Treatment effect on overall survival, according to baseline subgroups.



[a] Stratification factor.

CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; IC, investigator's choice; Nivo, nivolumab.

Supplementary Fig. 3. Overall survival in PD-L1 non-expressors at the 1-year follow-up (A) and primary analysis (B).

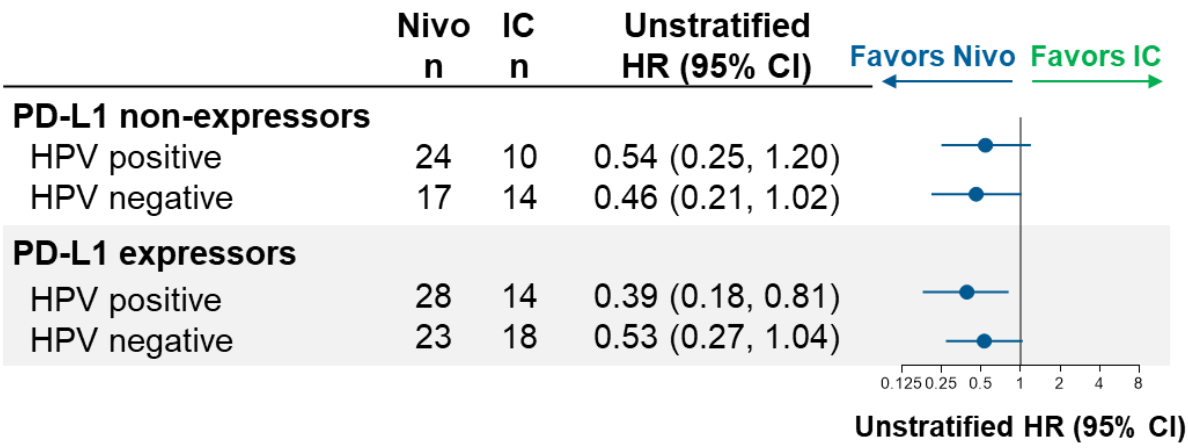


PD-L1 <1%	Median OS, mo (95% CI)	HR (95% CI)
Nivolumab	6.1 (4.4, 10.3)	0.83 (0.54, 1.29)
IC	5.5 (3.7, 8.5)	

PD-L1 <1%	Median OS, mo (95% CI)	HR (95% CI)
Nivolumab	5.7 (4.4, 12.7)	0.89 (0.54, 1.45)
IC	5.8 (4.0, 9.8)	

Symbols represent censored observations
CI, confidence interval; HR, hazard ratio; IC, investigator's choice; Nivo, nivolumab; OS, overall survival; PD-L1, programmed death ligand 1.

Supplementary Fig. 4. Treatment effect on overall survival by tumor PD-L1 expression and HPV status.



CI, confidence interval; HPV, human papillomavirus; HR, hazard ratio; IC, investigator's choice; Nivo, nivolumab; PD-L1, programmed death ligand 1.