# Nivolumab versus investigator's choice in patients with recurrent or metastatic squamous cell carcinoma of the head and neck: Efficacy and safety in CheckMate 141 by age

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## Abstract

**Objectives:** Many patients with squamous cell carcinoma of the head and neck (SCCHN) are 65 years old; comorbidities and other age-related factors may affect their ability to tolerate traditional chemotherapy. Nivolumab is the only immunotherapy to significantly improve overall survival (OS) versus investigator's choice (IC) of single-agent chemotherapy at primary analysis in a phase 3 trial (CheckMate 141) in patients with recurrent/metastatic SCCHN post-platinum therapy. In this post hoc analysis, we report efficacy and safety by age.

**Patients and methods:** Eligible patients were randomized 2:1 to nivolumab 3 mg/kg every 2 weeks (n = 240) or IC (methotrexate, docetaxel, or cetuximab n = 121). The primary endpoint of the trial was OS. For this analysis, outcomes were analyzed by age < 65 and 65 years. The data cut-off date was September 2017 (minimum follow-up 24.2 months).

**Results:** At baseline, 68 patients (28.3%) receiving nivolumab and 45 patients (37.2%) receiving IC were 65 years. Baseline characteristics were generally similar across age groups. OS and tumor response benefits with nivolumab versus IC were maintained regardless of age. The 30-month OS rates of 11.2% (< 65 years) and 13.0% ( 65 years) with nivolumab were more than tripled versus corresponding IC rates of 1.4% and 3.3%, respectively. The nivolumab arm had a lower rate of treatment-related adverse events versus IC regardless of age, consistent with the overall patient population.

**Conclusion:** In CheckMate 141, nivolumab resulted in a higher survival versus IC in patients < 65 and 65 years, with a manageable safety profile in both age groups.

**ClinicalTrials.gov:** NCT02105636.

### Keywords

Biomarkers; Nivolumab; Squamous cell carcinoma of the head and neck; Age; Phase 3 clinical trial

## Introduction

Over half of the 500,000 new cases of squamous cell carcinoma of the head and neck (SCCHN) worldwide occur in patients 65 years of age and older [1,2], and this is expected to increase as the population ages [3,4]. A high proportion of cases will go on to develop recurrent/metastatic disease [5,6], for which platinum-based chemotherapy with or without cetuximab or pembrolizumab can be used as first-line therapy for patients able to tolerate treatment [7-9].

Immune checkpoint inhibitors are a recent treatment strategy for patients with SCCHN and offer an opportunity for durable responses with a manageable safety profile [2]. Two programmed death-1 (PD-1) inhibitors, nivolumab and pembrolizumab, are currently approved for the treatment of patients with recurrent/metastatic SCCHN who experienced disease progression after platinum-based therapy. However, there are concerns that age-related decline in immune function may impact the activity of checkpoint inhibitors [10,11]. Some data have been reported for these agents in elderly patients with other solid tumors [11,12], and a recent publication of pembrolizumab in recurrent/metastatic SCCHN post-platinum therapy included limited data on efficacy by age [13].

At the primary analysis of the randomized, open-label, phase 3 CheckMate 141 trial (NCT02105636), nivolumab significantly improved overall survival (OS) versus investigator's choice (IC) of therapy in patients with recurrent/metastatic SCCHN who experienced tumor progression or recurrence within 6 months of platinum-based therapy administered in the adjuvant, primary (i.e. with radiation), recurrent, or metastatic setting; survival benefit was maintained at 1 and 2 years of follow-up irrespective of tumor programmed death ligand 1 (PD-L1) expression and human papillomavirus (HPV) status [14-16]. The safety profile of nivolumab was manageable, with fewer grade 3–4 treatment-related adverse events (TRAEs) compared with IC [15]. Here, we report a post hoc analysis of the efficacy and safety of nivolumab by age (< 65 and   65 years old) in patients with recurrent/metastatic SCCHN from CheckMate 141.

## Patients and methods

### Study design and patients

CheckMate 141 is a randomized, open-label, phase 3 trial; the detailed study design has been described previously [14]. Briefly, eligible patients were 18 years of age or older, had histologically confirmed, recurrent/metastatic SCCHN of the oral cavity, oropharynx, hypo-pharynx, 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 to receive nivolumab (3 mg/kg every 2 weeks) or standard single agent of IC (methotrexate 40–60 mg/m$^2$ weekly, docetaxel 30–10 mg/m$^2$ weekly, or cetuximab 400 mg/m$^2$ once, then 250 mg/m$^2$ weekly) and stratified by prior cetuximab treatment. 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 [15].

CheckMate 141 was conducted in accordance with the ethical principles in the Declaration of Helsinki. Written informed consent was obtained from all patients 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. Progression-free survival (PFS), defined as the time from randomization to first date of investigator-assessed progression, and objective response rate (ORR), defined as the proportion of randomized patients who achieved a best response of complete or partial response as per investigator assessment, were secondary endpoints; duration of objective response, defined as time from objective response until a progression event, was an exploratory endpoint. Tumor responses were evaluated every 6 weeks from week 9 until disease progression or treatment discontinuation using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 [17]. Safety was evaluated using the Common Terminology Criteria for Adverse Events, version 4.0, at each treatment visit and for 100 days after receipt of last dose. Adverse events with potential immunologic cause were characterized as select adverse events. Tumor PD-L1 expression and HPV status were assessed as previously described [14].

For this post hoc subgroup analysis, outcomes were analyzed by age (< 65 years and 65 years). This analysis is based on a September 2017 data cutoff, representing a minimum follow-up of 24.2 months (Supplementary Fig 1.).

### Statistical analyses

Efficacy analyses were conducted in patients < 65 and 65 years old in the intent-to-treat population; safety analyses were conducted in the same subgroups among patients who received at least one dose of treatment.

OS and PFS were estimated by the Kaplan-Meier method [18]; Cox proportional hazards models were used to estimate hazard ratios and corresponding two-sided 95% confidence intervals (CIs). A generalization of the Brookmeyer and Crowley method with a log-log transformation was used to compute CIs for median survival times [19], and a two-sided Cochran-Mantel-Haenszel test was used to compute the odds ratio and corresponding CIs for tumor response [20,21].

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## Results

### Patients and treatment

Of the 361 patients who underwent randomization, 68 of 240 patients in the nivolumab arm (28.3%) and 45 of 121 in the IC arm (37.2%) were 65 years old; 31 (12.9%) and 23 patients (19.0%), respectively, were 70 years old. Baseline characteristics were generally similar between patients < 65 years and 65 years old; notably, percentages of prior systemic therapy received were evenly matched between groups (Table 1).

Relative dosing intensity was comparable between the two age groups (< 65 and 65 years old) in the nivolumab arm (Supplementary Table 1). Median duration of therapy was similar between age groups in both the nivolumab and IC arms (1.6–1.9 months).

### Survival

Nivolumab resulted in a higher median OS compared with IC in patients < 65 years old (8.2 vs. 4.9 months, HR 0.63; 95% CI 0.47–0.84) and in patients  65 years old (6.9 vs. 6.0 months; HR 0.75; 95% CI 0.51–1.12; Fig. 1). Estimated OS rates at 12 months were higher in the nivolumab arms compared with IC in both age groups: 33.3% (95% CI 26.2–40.4) versus 19.7% (95% CI 11.5–29.6) in patients < 65 years old and 34.6% (95% CI 23.5–45.9) versus 20.0% (95% CI 9.9–32.6) in patients  65 years old. Similar results were observed at 30 months: OS rates with nivolumab were 11.2% (95% CI 6.7–16.9) in patients < 65 years old and 13.0% (95% CI 6.2–22.5) in patients  65 years old; corresponding rates with IC were 1.4% (95% CI 0.1–6.7) and 3.3% (95% CI 0.3–13.2), respectively. OS benefit with nivolumab was maintained irrespective of tumor PD-L1 expression levels and HPV status (Fig. 2) across both age groups.

Median PFS was similar in both treatment arms for patients < 65 years old (nivolumab, 2.0 months; IC, 2.7 months; HR 0.96; 95% CI 0.71–1.30) and for patients  65 years old (nivolumab, 2.1 months; IC, 2.0 months; HR 0.74; 95% CI 0.49–1.11), consistent with results in the overall study population (Fig. 3).

### Best overall response

Treatment with nivolumab resulted in higher ORR versus IC in both age groups (Table 2). In patients < 65 years old, ORRs for the nivolumab and IC arms were 12.8% and 6.6%, respectively; in patients  65 years old, ORRs were 14.7% and 4.4%, respectively, including three patients (4.4%) with complete responses and seven patients (10.3%) with partial responses in the nivolumab arm (Fig. 4). Among patients  65 years old receiving IC, 1 patient (2.2%) had a complete response and 1 patient (2.2%) had a partial response. Median duration of objective response in the nivolumab arm was 8.5 months for patients < 65 years old and was not reached for patients  65 years old.

### Safety

TRAEs are summarized in Table 3. Among patients < 65 years old, any grade and grade 3–4 TRAEs were reported in 63.7% and 16.1% of patients receiving nivolumab, respectively, and in 77.5% and 31.0% of patients receiving IC, respectively. Among patients who were  65 years old, any grade and grade 3–4 events were reported in 57.4% and 13.2%, respectively, of patients receiving nivolumab, and in 82.5% and 47.5%, respectively, of patients receiving IC. The most common select TRAEs in patients  65 years old in the nivolumab arm were skin-related (14 patients; 20.6%); no grade 3–4 select TRAEs were reported in this patient subgroup (Supplementary Table 2).

### Efficacy and safety among patients  70 years old

In patients  70 years old (nivolumab, n = 31; IC, n = 23), the efficacy of nivolumab treatment was consistent with that seen in patients  65 years old and in the overall patient population; median OS in this group was 4.8 months in the nivolumab arm compared with 4.6 months in the IC arm (HR 0.91; 95% CI 0.52–1.60). Median PFS was 2.1 months in the nivolumab arm compared with 2.3 months in the IC arm (HR 1.0; 95% CI 0.57–1.75). Among patients who were  70 years old, ORRs in the nivolumab and IC arms were 6.5%

and 8.7%, respectively. Any grade and grade 3–4 TRAEs were reported in 48.4% and 9.7%, respectively, of patients receiving nivolumab, and in 81.0% and 52.4%, respectively, of patients receiving IC.

## Discussion

In this post hoc analysis from CheckMate 141, the threshold of 65 years of age was chosen to maintain an optimal number of patients in each treatment arm; importantly, this cutoff also corresponds with established age classifications applied to patients with cancer [22,23]. While 70 years is also often used as the threshold for clinical trials in elderly patients [24,25], in CheckMate 141, patient numbers with this cutoff were too small for meaningful analyses. Nivolumab therapy resulted in an OS benefit compared with IC and responses were durable in patients with recurrent/metastatic SCCHN across both age groups of < 65 and 65 years old at a minimum follow-up of 2 years. Among patients 65 years old in the nivolumab arm, ORR was 14.7% with 10 patients experiencing complete or partial responses. The median OS for this subgroup was 6.9 months and 13.0% of patients were still alive at 30 months, nearly triple that of patients in the IC arm. Although the number of patients 70 years old was limited (31 in the nivolumab arm and 23 in the IC arm), the efficacy and safety of nivolumab in these patients were consistent with results seen in patients 65 years old.

These data in the elderly population of CheckMate 141 are comparable to those previously reported in the primary analysis and 2-year update to the study [14,15]. At 2 years, the ORR for patients receiving nivolumab was 13.3%; median OS was 7.7 months with 16.9% of patients still alive at 24 months [15]. OS benefit was maintained with nivolumab irrespective of tumor PD-L1 expression levels and HPV status, and this finding is consistent with results presented in the current analysis across age groups. Even though no clear difference could be observed in patients 65 years without PD-L1–expressing tumors, the number of patients in this subgroup was small. Results were recently published from the phase 3 KEYNOTE-040 study comparing pembrolizumab versus methotrexate, docetaxel or cetuximab [13].

Age-related immune dysfunction, attributed to both cellular components of the immune system as well as changes in the tumor microenvironment, is a key challenge in developing effective immunotherapies for elderly patients [26,27]. Immunosenescence is thought to impair the antitumor immune response through reduced tumor antigen release, altered antigen-uptake and antigen-presenting functions, and impaired T-cell activation and trafficking, all of which can hinder the elimination of tumor cells [28]. However, tumor mutational burden, which has been shown to increase with age, among other factors, leads to increased neoantigen formation and subsequent increased immune response [29]. The greater immunogenicity of tumors with high tumor mutational burden makes them a target for immuno-oncology therapies [30,31]. Advanced age may also exacerbate treatment-related toxicities due to metabolic changes, polypharmacy, and comorbidities [32], thereby limiting therapeutic options. A higher prevalence of adverse events such as nephrotoxicity, thrombocytopenia, and myelosuppression is associated with chemotherapy in elderly patients [33,34]. In contrast, nivolumab was well tolerated in the current study, and the incidence and severity of TRAEs were comparable among patients in both age

groups. The most common associated adverse events in patients ≥65 years old were fatigue, decreased appetite, and diarrhea, similar to those reported in the overall study population [14,15].

A meta-analysis was recently published using random-effects estimates to evaluate the efficacy of PD-1 and PD-L1 inhibitors in patients ≥65 years old with advanced solid tumors, including clinical studies of nivolumab in non-small cell lung cancer, renal cell carcinoma, and melanoma [35]. Similar to the results of the current analysis, a consistent improvement in survival associated with the use of these therapies across groups of younger and older patients was reported. A retrospective study of PD-1 and PD-L1 inhibitors in patients with melanoma also found no significant differences in toxicity between younger and older age groups, although there was a trend toward a higher rate of endocrine-related events in elderly patients [11].

The current analysis addresses an unmet need for data among elderly patients with SCCHN. Elderly patients are often underrepresented in clinical trials [2,36,37], which contributes to this increasing need given the changing demographics of head and neck cancer. In clinical trials specific to elderly patients, treatment selection is often based on fitness or geriatric evaluation as frailty can vary among patients considered to be elderly [24,37-39]. The current study did not assess frailty before enrollment; however, patients randomized to the IC arm of this study were considered able and fit to undergo chemotherapy (including taxane) or treatment with cetuximab. While limited by the post hoc nature of the analysis, our results highlight the opportunity for new interventions to improve outcomes and minimize toxicities in elderly patients with SCCHN.

## Conclusion

Here, we show that nivolumab therapy demonstrated efficacy benefit, durable response, and a manageable safety profile in patients ≥65 years old with SCCHN, suggesting that age should not be a critical factor when selecting second-line immunotherapy. These data support the use of nivolumab in younger and older patients with recurrent/metastatic SCCHN post-platinum therapy.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgements

## Abbreviations:

| | |
|---|---|
| **CI** | confidence interval |
| **ECOG** | Eastern Cooperative Oncology Group |
| **HPV** | human papillomavirus |
| **HR** | hazard ratio |
| **IC** | investigator's choice |
| **NR** | not reached |
| **ORR** | objective response rate |
| **OS** | overall survival |
| **PD-1** | programmed death-1 |
| **PD-L1** | programmed death ligand 1 |
| **PFS** | progression-free survival |
| **SCCHN** | squamous cell carcinoma of the head and neck |
| **TRAE** | treatment-related adverse event |

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**A**

Patients <65 Years Old

| <65 years | Median OS, mo (95% CI) | HR (95% CI) |
|---|---|---|
| Nivolumab (n = 172) | 8.2 (6.1–9.1) | 0.63 (0.47–0.84) |
| IC (n = 76) | 4.9 (3.9–5.8) | |

No. at risk

| | 0 | 3 | 6 | 9 | 12 | 15 | 18 | 21 | 24 | 27 | 30 | 33 | 36 | 39 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| NIVO | 172 | 124 | 97 | 71 | 55 | 41 | 36 | 30 | 26 | 19 | 9 | 6 | 3 | 0 |
| IC | 76 | 55 | 28 | 18 | 14 | 7 | 5 | 4 | 3 | 1 | 1 | 1 | 0 | 0 |

**B**

Patients ≥65 Years Old

| ≥65 years | Median OS, mo (95% CI) | HR (95% CI) |
|---|---|---|
| Nivolumab (n = 68) | 6.9 (4.0–9.7) | 0.75 (0.51–1.12) |
| IC (n = 45) | 6.0 (4.0–7.5) | |

No. at risk

| | 0 | 3 | 6 | 9 | 12 | 15 | 18 | 21 | 24 | 27 | 30 | 33 | 36 | 39 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| NIVO | 68 | 45 | 35 | 27 | 23 | 16 | 14 | 12 | 11 | 9 | 6 | 4 | 1 | 0 |
| IC | 45 | 33 | 23 | 14 | 9 | 7 | 5 | 4 | 4 | 3 | 0 | 0 | 0 | 0 |

**Fig. 1.**
Overall survival (OS) in patients (A) < 65 years old and (B)  65 years old. Abbreviations:
CI = confidence interval; HR = hazard ratio; IC = investigator's choice; NIVO = nivolumab.

**Fig. 2.**
Overall survival (OS) by (A, B) tumor programmed death ligand 1 (PD-L1) expression and (C, D) human papillomavirus (HPV) status.

**A**

Patients <65 Years Old



| <65 years | Median PFS, mo (95% CI) | HR (95% CI) |
|---|---|---|
| Nivolumab (n = 172) | 2.0 (1.9–2.1) | 0.96 (0.71–1.30) |
| IC (n = 76) | 2.7 (2.0–3.2) | |

No. at risk

| | 0 | 3 | 6 | 9 | 12 | 15 | 18 | 21 | 24 | 27 | 30 | 33 | 36 | 39 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| NIVO | 172 | 56 | 30 | 20 | 12 | 11 | 11 | 10 | 7 | 4 | 2 | 0 | 0 | 0 |
| IC | 76 | 28 | 5 | 2 | 2 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

**B**

Patients ≥65 Years Old



| ≥65 years | Median PFS, mo (95% CI) | HR (95% CI) |
|---|---|---|
| Nivolumab (n = 68) | 2.1 (1.9–3.2) | 0.74 (0.49–1.11) |
| IC (n = 45) | 2.0 (1.9–3.3) | |

No. at risk

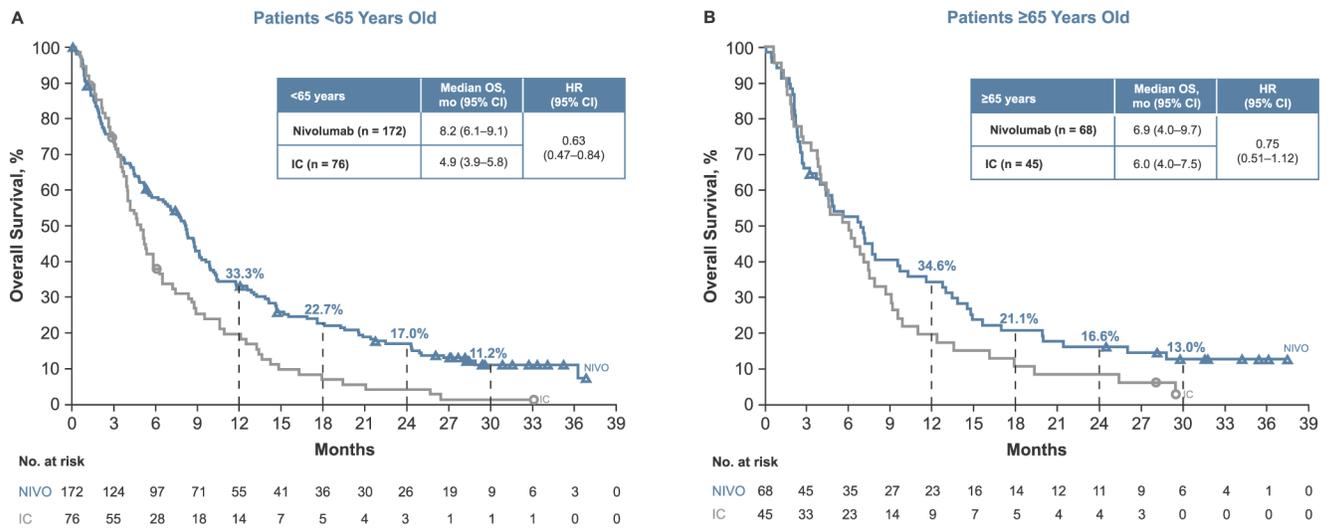| | 0 | 3 | 6 | 9 | 12 | 15 | 18 | 21 | 24 | 27 | 30 | 33 | 36 | 39 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| NIVO | 68 | 26 | 13 | 9 | 7 | 6 | 6 | 6 | 6 | 4 | 3 | 3 | 1 | 0 |
| IC | 45 | 16 | 5 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

**Fig. 3.**

Progression-free survival (PFS) in patients (A) < 65 years old and (B) 65 years old.

Abbreviations: CI = confidence interval; HR = hazard ratio; IC = investigator's choice; NIVO = nivolumab.
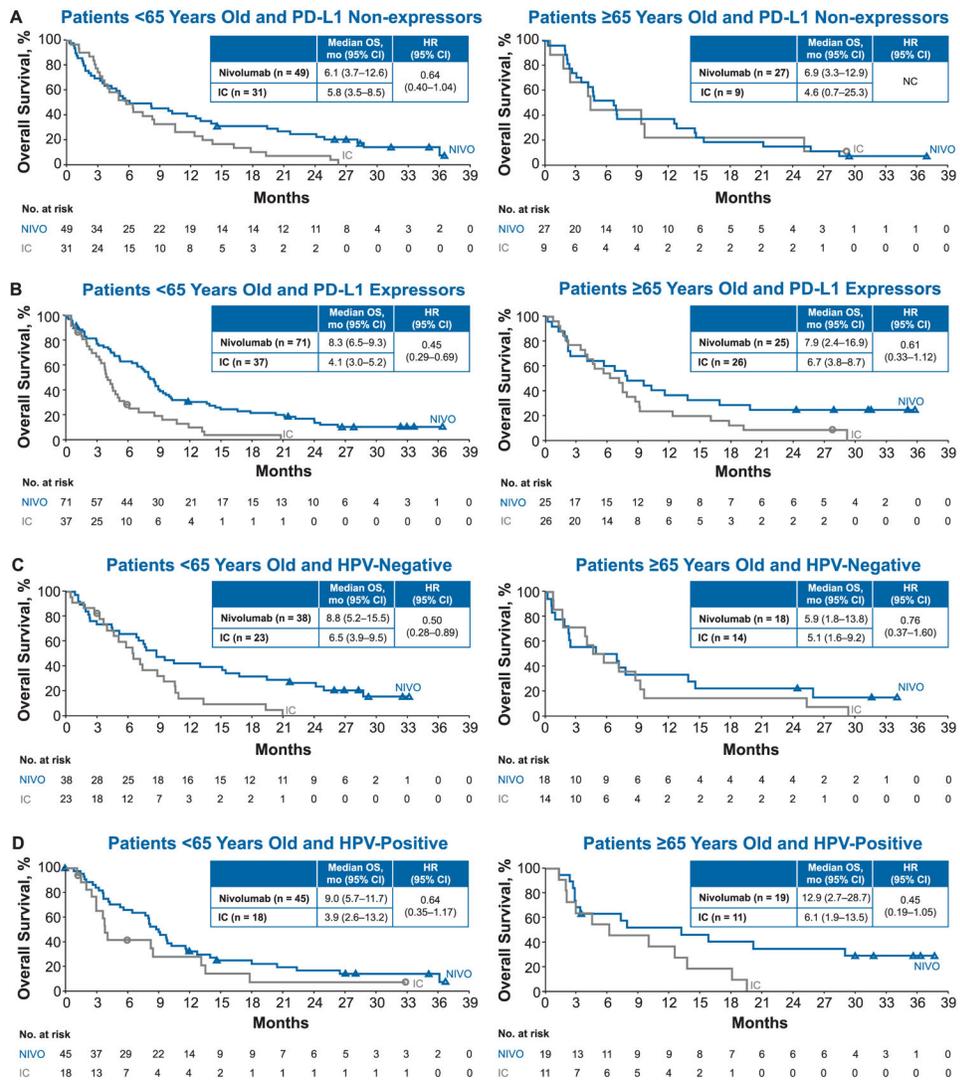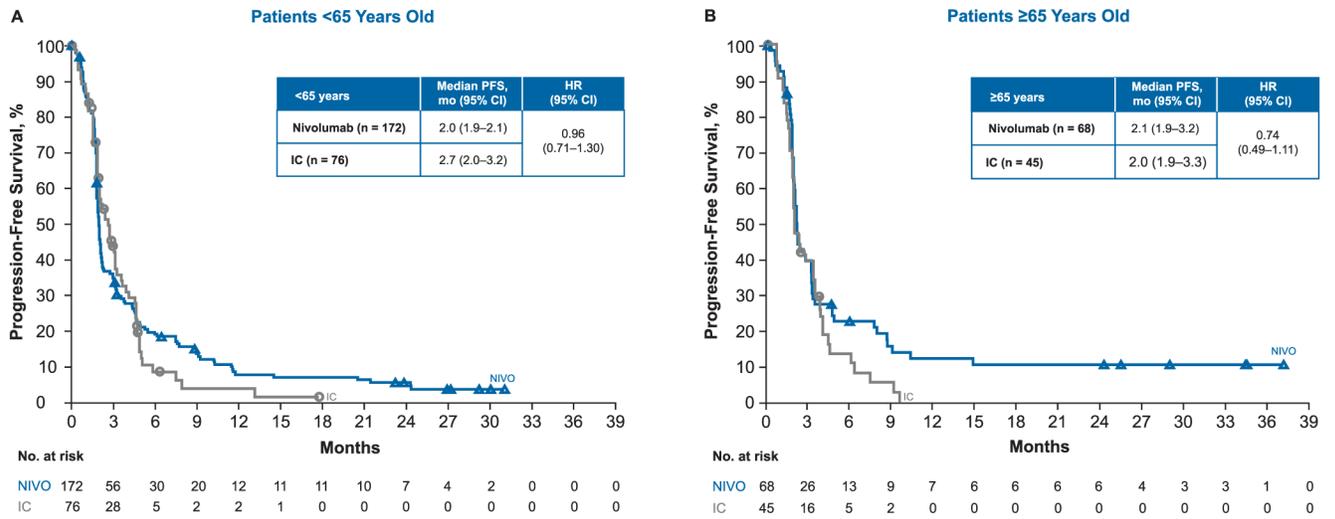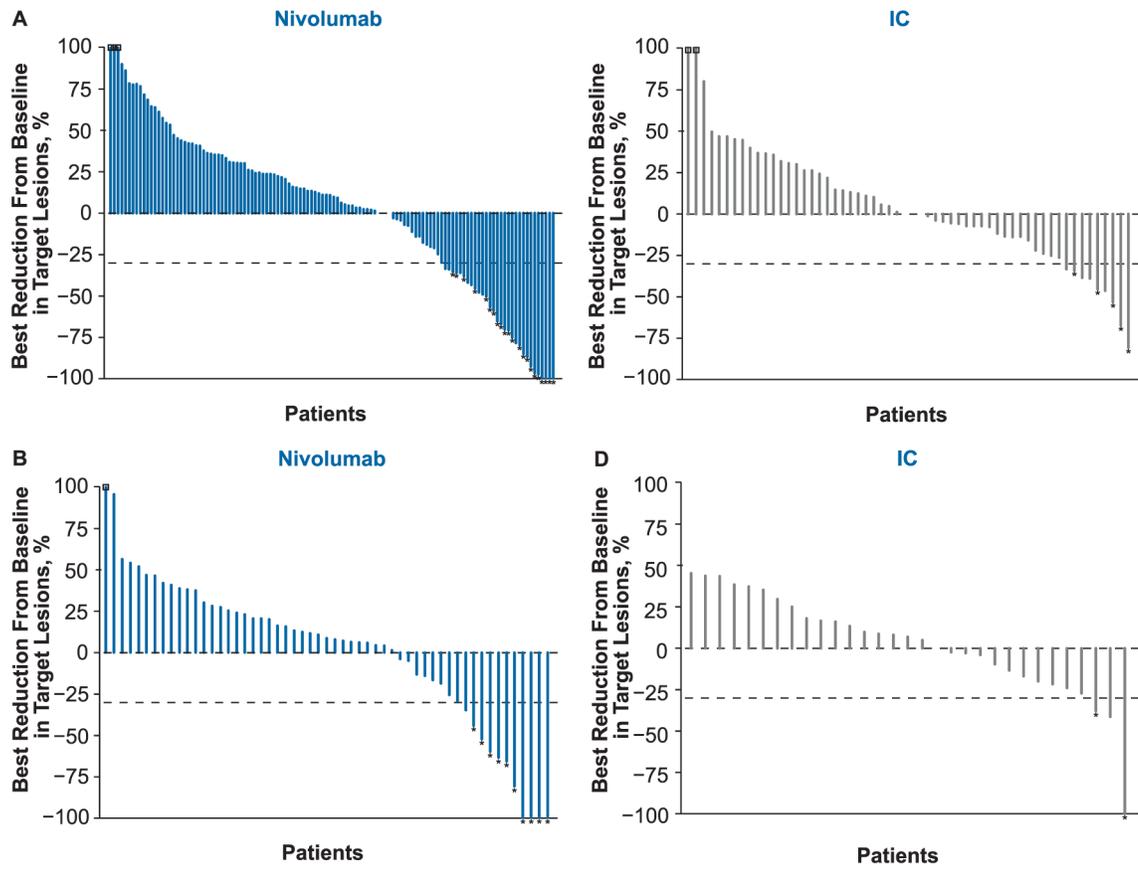
**Fig. 4.**
Best reduction from baseline in target lesions in patients (A) < 65 years old and (B) 65 years old. Abbreviation: * = responders; square symbol = % change truncated to 100%; IC = investigator's choice.

**Table 1**

Baseline characteristics.

| Patients, n (%) | < 65 Years | | 65 Years | |
|---|---|---|---|---|
| | Nivolumab (n = 172) | IC (n = 76) | Nivolumab (n = 68) | IC (n = 45) |
| Sex, male | 134 (77.9) | 67 (88.2) | 63 (92.6) | 36 (80.0) |
| Race | | | | |
| White | 139 (80.8) | 66 (86.8) | 57 (83.8) | 38 (84.4) |
| Black or African American | 8 (4.7) | 2 (2.6) | 2 (2.9) | 1 (2.2) |
| Asian | 20 (11.6) | 8 (10.5) | 9 (13.2) | 6 (13.3) |
| Other | 5 (2.9) | 0 | 0 | 0 |
| ECOG performance status | | | | |
| 0 | 40 (23.3) | 16 (21.1) | 9 (13.2) | 7 (15.6) |
| 1 | 132 (76.7) | 56 (73.7) | 57 (83.8) | 38 (84.4) |
| 2 | 0 | 3 (3.9) | 1 (1.5) | 0 |
| Not reported | 0 | 1 (1.3) | 1 (1.5) | 0 |
| Region | | | | |
| North America | 76 (44.2) | 28 (36.8) | 25 (36.8) | 16 (35.6) |
| Europe | 75 (43.6) | 39 (51.3) | 34 (50.0) | 23 (51.1) |
| Rest of world | 21 (12.2) | 9 (11.8) | 9 (13.2) | 6 (13.3) |
| Tobacco use | | | | |
| Current/former | 135 (78.5) | 57 (75.0) | 56 (82.4) | 29 (64.4) |
| Never | 28 (16.3) | 17 (22.4) | 11 (16.2) | 14 (31.1) |
| Unknown | 9 (5.2) | 2 (2.6) | 1 (1.5) | 2 (4.4) |
| Site of primary tumor | | | | |
| Oral cavity | 85 (49.4) | 42 (55.3) | 23 (33.8) | 25 (55.6) |
| Pharynx | 66 (38.4) | 24 (31.6) | 26 (38.2) | 13 (28.9) |
| Larynx | 18 (10.5) | 8 (10.5) | 16 (23.5) | 6 (13.3) |
| Other | 3 (1.7) | 2 (2.6) | 3 (4.4) | 1 (2.2) |
| HPV status | | | | |
| Positive | 45 (26.2) | 18 (23.7) | 19 (27.9) | 11 (24.4) |
| Negative | 38 (22.1) | 23 (30.3) | 18 (26.5) | 14 (31.1) |
| Unknown/not reported | 89 (51.7) | 35 (46.1) | 31 (45.6) | 20 (44.4) |
| PD-L1 expression | | | | |
| 1% | 71 (41.3) | 37 (48.7) | 25 (36.8) | 26 (57.8) |
| < 1% | 49 (28.5) | 31 (40.8) | 27 (39.7) | 9 (20.0) |
| Lines of prior systemic cancer therapy | | | | |
| 1 | 73 (42.4) | 33 (43.4) | 33 (48.5) | 25 (55.6) |
| 2 | 62 (36.0) | 31 (40.8) | 18 (26.5) | 13 (28.9) |
| 3 | 37 (21.5) | 12 (15.8) | 17 (25.0) | 7 (15.6) |
| Prior systemic therapy received[a] | | | | |
| Platinum-based therapy | 172 (100.0) | 76 (100.0) | 68 (100.0) | 45 (100.0) |

| Patients, n (%) | < 65 Years | | 65 Years | |
|---|---|---|---|---|
| | **Nivolumab (n = 172)** | **IC (n = 76)** | **Nivolumab (n = 68)** | **IC (n = 45)** |
| Monoclonal antibody | 113 (65.7) | 45 (59.2) | 40 (58.8) | 28 (62.2) |
| Folic acid analog | 5 (2.9) | 3 (3.9) | 2 (2.9) | 0 |
| Taxane | 97 (56.4) | 41 (53.9) | 35 (51.5) | 21 (46.7) |
| Other – approved | 107 (62.2) | 51 (67.1) | 33 (48.5) | 18 (40.0) |
| Other – experimental | 19 (11.0) | 7 (9.2) | 4 (5.9) | 7 (15.6) |

[a]Some patients may have been treated with more than one type of therapy. Abbreviations: ECOG = Eastern Cooperative Oncology Group; HPV = human papillomavirus; IC = investigator's choice; PD-L1 = programmed death ligand 1.

**Table 2**

Best overall response per investigator. Abbreviations: + = censored value; CI = confidence interval; IC = investigator's choice; NR = not reached; ORR = objective resDonse rate.

| | < 65 Years | | 65 Years | |
| --- | --- | --- | --- | --- |
| | Nivolumab (n = 172) | IC (n = 76) | Nivolumab (n = 68) | IC (n = 45) |
| Best overall response, n (%) | | | | |
| Complete response | 4 (2.3) | 0 | 3 (4.4) | 1 (2.2) |
| Partial response | 18 (10.5) | 5 (6.6) | 7 (10.3) | 1 (2.2) |
| Stable disease | 36 (20.9) | 31 (40.8) | 19 (27.9) | 12 (26.7) |
| Progressive disease | 72 (41.9) | 25 (32.9) | 27 (39.7) | 17 (37.8) |
| Unable to determine | 42 (24.4) | 15 (19.7) | 12 (17.6) | 14 (31.1) |
| ORR, n (%) | 22 (12.8) | 5 (6.6) | 10 (14.7) | 2 (4.4) |
| [95% CI] | [8.2–18.7] | [2.2–14.7] | [7.3–25.4] | [0.5–15.1] |
| Time to objective response among responders, median (range), mo | 2.1 (1.8–7.4) | 2.0 (1.9–2.0) | 2.1 (1.8–6.3) | 3.5 (2.3–4.6) |
| Duration of response among responders, median (range), mo | 8.5 (2.8 to 28.0+) | 3.0 (2.7+ to 11.3) | NR (2.8 to 32.8+) | 4.9 (1.5+ to 4.9) |

**Table 3**

Treatment-related adverse events (TRAEs) in ≥ 10% of patients. Abbreviation: IC = investigator's choice.

| | <65 Years | | | | 65 Years | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| | Nivolumab (n = 168) | | IC (n = 71) | | Nivolumab (n = 68) | | IC (n = 40) | |
| | Any Grade | Grade 3–4 | Any Grade | Grade 3–4 | Any Grade | Grade 3–4 | Any Grade | Grade 3–4 |
| Any TRAE, n (%) | 107 (63.7) | 27 (16.1) | 55 (77.5) | 22 (31.0) | 39 (57.4) | 9 (13.2) | 33 (82.5) | 19 (47.5) |
| Fatigue | 24 (14.3) | 3 (1.8) | 14 (19.7) | 1 (1.4) | 13 (19.1) | 2 (2.9) | 6 (15.0) | 2 (5.0) |
| Nausea | 17 (10.1) | 0 | 16 (22.5) | 1 (1.4) | 5 (7.4) | 0 | 7 (17.5) | 0 |
| Rash | 14 (8.3) | 0 | 1 (1.4) | 0 | 5 (7.4) | 0 | 4 (10.0) | 1 (2.5) |
| Diarrhea | 13 (7.7) | 1 (0.6) | 7 (9.9) | 1 (1.4) | 7 (10.3) | 0 | 9 (22.5) | 1 (2.5) |
| Decreased appetite | 11 (6.5) | 0 | 6 (8.5) | 0 | 8 (11.8) | 0 | 2 (5.0) | 0 |
| Anemia | 8 (4.8) | 2 (1.2) | 13 (18.3) | 3 (4.2) | 4 (5.9) | 1 (1.5) | 6 (15.0) | 3 (7.5) |
| Asthenia | 8 (4.8) | 0 | 12 (16.9) | 2 (2.8) | 2 (2.9) | 1 (1.5) | 5 (12.5) | 0 |
| Vomiting | 6 (3.6) | 0 | 4 (5.6) | 0 | 2 (2.9) | 0 | 4 (10.0) | 0 |
| Mucosal inflammation | 4 (2.4) | 0 | 9 (12.7) | 1 (1.4) | 0 | 0 | 6 (15.0) | 1 (2.5) |
| Stomatitis | 2 (1.2) | 1 (0.6) | 8 (11.3) | 2 (2.8) | 4 (5.9) | 0 | 4 (10.0) | 1 (2.5) |
| Alopecia | 0 | 0 | 10 (14.1) | 0 | 0 | 0 | 4 (10.0) | 0 |