

Long-term Outcomes with Nivolumab as First-line Treatment in Recurrent or Metastatic Head and Neck Cancer: Subgroup Analysis of CheckMate 141

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Abstract

In the randomized, phase 3 CheckMate 141 trial, nivolumab significantly improved overall survival (OS) versus investigator's choice (IC) of chemotherapy at primary analysis among 361 patients with recurrent or metastatic squamous cell carcinoma of the head and neck (R/M SCCHN) post-platinum therapy. Nivolumab versus IC as first-line treatment also improved OS among patients with R/M SCCHN who progressed on platinum therapy for locally advanced disease in the adjuvant or primary setting at 1-year follow-up. In the present long-term follow-up analysis of patients receiving first-line treatment, OS benefit with nivolumab ($n = 50$) versus IC ($n = 26$) was maintained (median: 7.7 months versus 3.3 months; hazard ratio: 0.56; 95% confidence interval, 0.34-0.94) at 2 years. No new safety signals were identified. In summary, this long-term 2-year analysis of CheckMate 141 supports the use of nivolumab as a first-line treatment for patients with platinum-refractory R/M SCCHN.

Key words: clinical trial; squamous cell carcinoma of head and neck; nivolumab; immunotherapy.

Introduction

In the primary analysis of CheckMate 141 (NCT02105636), nivolumab significantly improved overall survival (OS) compared with the investigator's choice (IC) of chemotherapy, among patients with recurrent or metastatic squamous cell carcinoma of the head and neck (R/M SCCHN) who

experienced disease progression on or within 6 months after platinum-based therapy.¹ An exploratory analysis demonstrated that nivolumab stabilized quality of life versus IC, which was associated with clinically meaningful deterioration.² OS benefit with nivolumab was maintained at 2 years of follow-up.³ Nivolumab also improved OS versus

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IC as first-line treatment among a subgroup of patients with R/M SCCHN who progressed on or within 6 months after platinum-based therapy for locally advanced disease in the adjuvant or primary (ie, with radiation) setting (hereafter referred to as first-line treatment for R/M SCCHN) at 1-year follow-up.⁴ Here, we report long-term outcomes among patients receiving first-line treatment for R/M SCCHN at 2 years of follow-up.

Patients and Methods

CheckMate 141 was an open-label, phase 3 study in which patients were randomized to nivolumab (3 mg/kg every 2 weeks) or IC (methotrexate, docetaxel, or cetuximab)¹; the full study design has been described previously.^{1,4} OS was the primary endpoint; progression-free survival (PFS), objective response rate (ORR), and safety were also evaluated. The current post hoc subgroup analysis was performed in patients receiving first-line treatment in CheckMate 141 (data cutoff: September 2017, representing a minimum duration of follow-up of 24.2 months for the study). Efficacy was assessed in the intent-to-treat patient population and safety in all treated patients.

CheckMate 141 was registered with the National Cancer Institute. Institutional review boards at participating sites approved the study protocol. Patients provided written informed consent before enrollment.

Results

Of 361 patients randomized in CheckMate 141, 76 patients (21.0%; nivolumab, *n* = 50 and IC, *n* = 26) constituted the first-line intent-to-treat population; of these, 74 (nivolumab, *n* = 49 and IC, *n* = 25) received treatment.

The baseline characteristics of patients receiving first-line treatment in CheckMate 141 (Supplementary Table 1) were generally similar to those of the overall population.¹ The median duration of treatment was 1.9 months for the

nivolumab arm and ranged between 1.6 and 2.0 months for IC. At data cutoff, 45 nivolumab-treated patients (91.8%) and 25 IC-treated patients (100.0%) had discontinued treatment, primarily due to disease progression (Supplementary Table 2). After treatment discontinuation, cetuximab was the most common second-line treatment in the nivolumab arm (5 patients [10.0%]), whereas fluorouracil was most common in the IC arm (3 patients [11.5%]); Supplementary Table 3).

At 2-year follow-up, among patients who received first-line treatment for R/M SCCHN, nivolumab prolonged OS versus IC (median, 7.7 months versus 3.3 months; hazard ratio [HR], 0.56; 95% confidence interval [CI], 0.34–0.94) (Figure 1). The 24-month OS rates were 20.4% with nivolumab versus 3.8% with IC. Median PFS was 2.1 months (nivolumab) versus 2.3 months (IC) (HR, 0.79; 95% CI, 0.47–1.34); 24-month PFS rates were 14.8% versus 0%, respectively (Figure 2). Responses were reported in 10 patients (nivolumab) versus 3 patients (IC), resulting in an ORR of 20.0% versus 11.5%, respectively (Supplementary Table 4). The median time to response was approximately 2 months in both arms; the median duration of response was not reached with nivolumab. Two of the 10 patients with response to nivolumab were receiving treatment as of data cutoff; all 3 patients with response to IC had discontinued treatment.

Any-grade treatment-related adverse events (TRAEs) with the time of onset ≤1 year since the start of treatment occurred in 34 nivolumab-treated patients (69.4%) versus 18 IC-treated patients (72.0%), with grade 3–4 TRAEs in 13 patients (26.5%) versus 9 patients (36.0%), respectively (Supplementary Table 5). TRAEs with the time of onset >1 year occurred in 6 nivolumab-treated patients (12.2%) versus one IC-treated patient (4.0%). Select TRAEs are summarized in Supplementary Table 5.

Discussion

In this 2-year follow-up of patients receiving first-line treatment for R/M SCCHN, despite being a group with a poorer

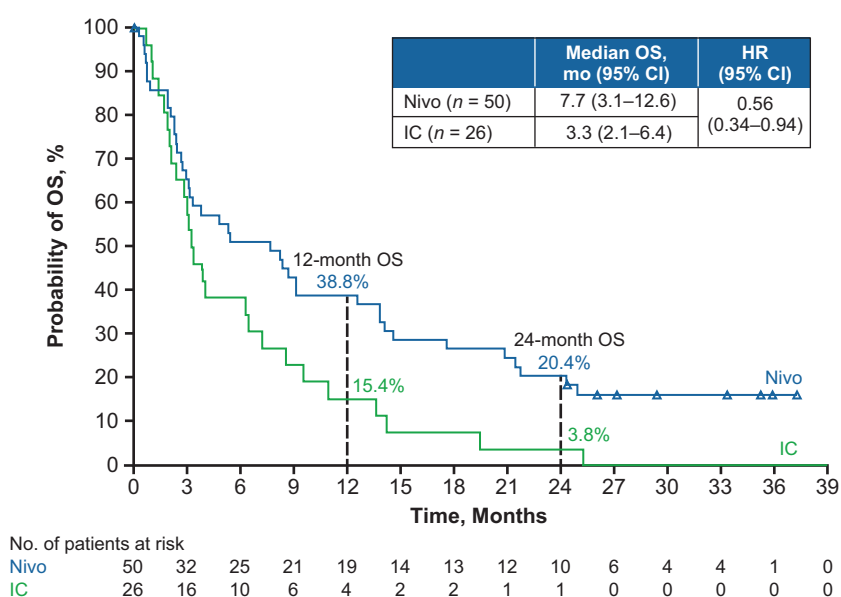


Figure 1. OS among patients randomized to nivolumab or IC as first-line treatment for recurrent or metastatic squamous cell carcinoma of the head and neck after progressing on or after platinum therapy (within 6 months) in the adjuvant or primary (ie, with radiation) setting for locally advanced disease. Abbreviations: CI, confidence interval; HR, hazard ratio; IC, investigator’s choice; mo, months; Nivo, nivolumab; OS, overall survival.

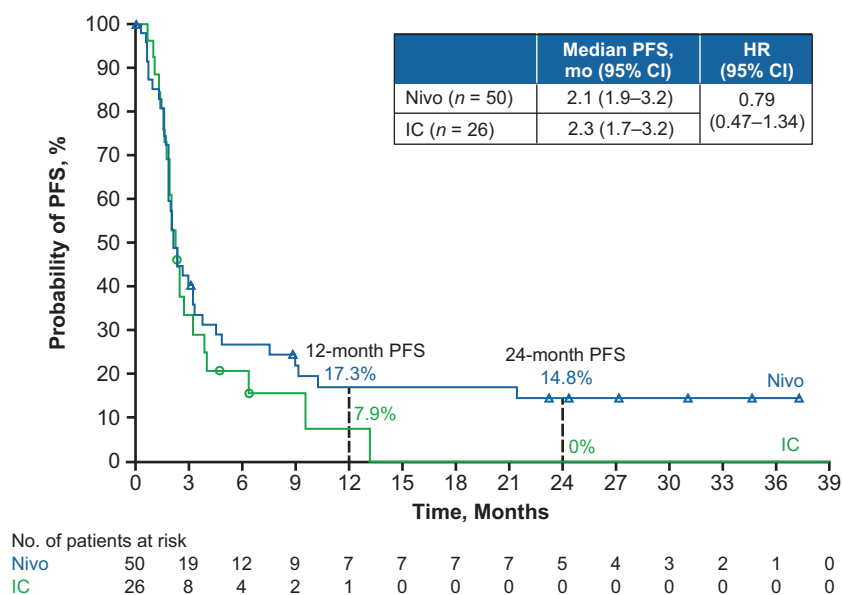


Figure 2. PFS among patients randomized to nivolumab or IC as first-line treatment for recurrent or metastatic squamous cell carcinoma of the head and neck after progressing on or after platinum therapy (within 6 months) in the adjuvant or primary (ie, with radiation) setting for locally advanced disease. Abbreviations: CI, confidence interval; HR, hazard ratio; IC, investigator's choice; mo, months; Nivo, nivolumab; PFS, progression-free survival.

prognosis, results were consistent with the primary analysis in the overall population of CheckMate 141. The OS benefit of first-line treatment with nivolumab versus IC that was seen at 1-year follow-up was maintained, with clinically meaningful differences in 2-year OS and PFS rates between the 2 treatment arms. No new safety signals were identified. Based on programming corrections that were implemented to more accurately identify patients who had received first-line treatment for R/M SCCHN, it was determined that 2 of 52 patients in the nivolumab arm of the 1-year analysis were incorrectly categorized as having received first-line treatment; the current analysis thus included 50 patients in the nivolumab arm.⁴

Until recently, the standard of care for first-line treatment of unresectable R/M SCCHN was the EXTREME regimen (cetuximab, platinum, and 5-fluorouracil).^{5,6} In 2019, it was shown that OS associated with TPEX (cetuximab, platinum, and docetaxel) and EXTREME was not significantly different; however, the TPEX regimen was associated with significantly lower toxicity.⁷ Also in 2019, pembrolizumab as monotherapy (among patients with programmed death-ligand 1 combined positive score [CPS] ≥ 1) and in combination with 5-fluorouracil and platinum was shown to improve OS versus EXTREME and was approved across the world for the first-line treatment of platinum-eligible patients with unresectable R/M SCCHN.^{5,8} While nivolumab plus ipilimumab versus EXTREME did not statistically improve OS in all randomized patients and patients with CPS ≥ 20 in CheckMate 651 (NCT02741570), dual checkpoint inhibition showed evidence of clinical benefit (prolonged OS and durable response) and a favorable safety profile versus EXTREME in patients with R/M SCCHN with CPS ≥ 20 or CPS ≥ 1 .⁹

Until recently, first-line treatment options for patients with platinum-refractory R/M SCCHN, such as those enrolled in CheckMate 141, were limited primarily to the IC options of CheckMate 141, ie, methotrexate, taxanes, or cetuximab; these are associated with poorer OS compared with nivolumab, as shown in CheckMate 141.¹ With the approval of nivolumab and pembrolizumab for the treatment

of platinum-refractory R/M SCCHN, programmed death-1 inhibitors have become the standard of care in this patient population.⁵ The number of patients in this analysis was small; nonetheless, the results at 2 years of follow-up are promising given the limited treatment options in this hard-to-treat patient population. We note that the group of platinum-refractory patients included in this analysis would not have been eligible for the KEYNOTE-048 trial, which excluded patients with progression within 6 months of curative intent therapy.⁸ These data therefore uniquely support the use of nivolumab monotherapy as first-line treatment in patients with platinum-refractory R/M SCCHN.

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Conflict of Interest

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Author Contributions

Conception/Design: Gillison, Blumenschein, Fayette, Guigay, Harrington, Tahara, Ferris. Collection and/or assembly of data: Gillison, Blumenschein, Fayette, Guigay, Colevas, Licitra, Harrington, Kasper, Vokes, Even, Worden, Saba, Iglesias Docampo, Haddad, Rordorf, Kiyota, Tahara, Ferris. Data analysis and interpretation: All authors. Manuscript Writing: All authors. Final approval of manuscript: All authors.

Data Availability

The data underlying this article will be shared on reasonable request to the corresponding author.

Supplementary Material

Supplementary material is available at *The Oncologist* online.

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