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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Abstract

Nivolumab significantly improved overall survival (OS) vs investigator's choice (IC) of chemotherapy at the primary analysis of randomized, open-label, phase 3 CheckMate 141 in patients with recurrent or metastatic (R/M) squamous cell carcinoma of the head and neck (SCCHN). Here, we report that OS benefit with nivolumab was maintained at a minimum follow-up of 11.4 months. Further, OS benefit with nivolumab vs IC was also noted among patients who received first-line treatment for R/M SCCHN after progress-ing on platinum therapy for locally advanced disease in the adjuvant or primary (i.e., with radiation) setting. The Oncol-ogist 2018;23:1–4

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 versus 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 5 .01) at primary analysis in the overall study popula-tion [6]. Here, we report outcomes among patients who received nivolumab versus 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 radia-tion) 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.

Materials and 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, doce-taxel, 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 analy-sis, efficacy and safety were assessed in patients receiving nivolu-mab versus IC as first-line treatment for R/M SCCHN. Updated results in the overall intent-to-treat population, based on a data-base 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 Insti-tute and approved by the institutional board at each participating site. All patients provided informed consent prior to enrollment.

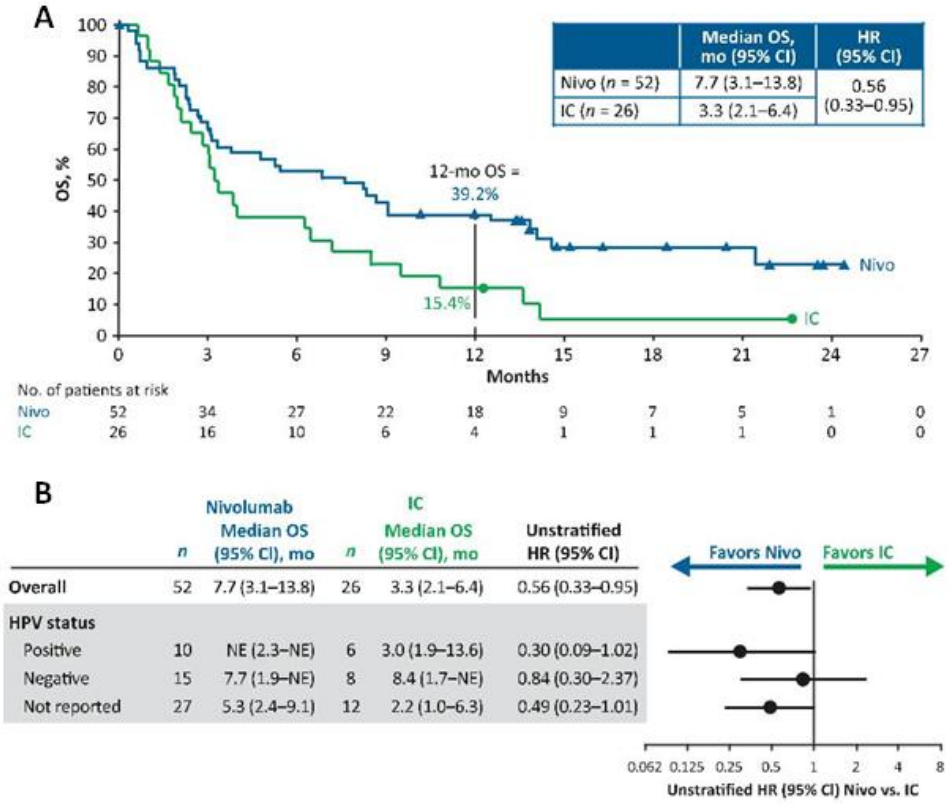

Figure 1. Survival among patients randomized to nivolumab or IC as first-line treatment for R/M SCCHN after progressing on or after plati-num therapy (within 6 months) in the adjuvant or primary (i.e., with radiation) setting for locally advanced disease: Kaplan-Meier plot of OS (A) and treatment effect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

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

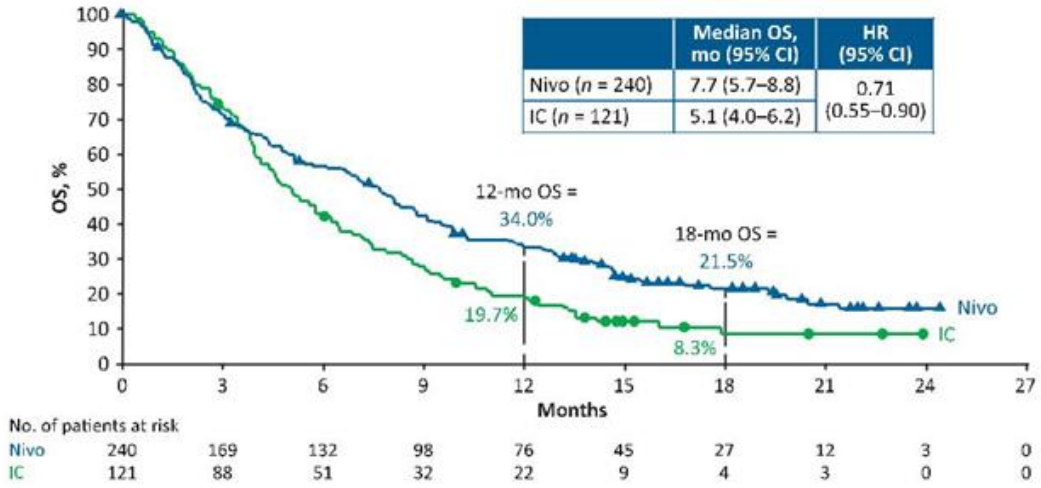

Figure 2. Kaplan-Meier plot of OS in the overall intent-to-treat population.

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

Results

First-Line Treatment for R/M SCCHN

In all, 78 patients (21.6%) received nivolumab (n 5 52) or IC (n 5 26) as first-line treatment for R/M SCCHN. The baseline characteristics of these patients (supplemental online Table 1) were similar to those of the overall population [6].

Nivolumab as first-line treatment improved OS versus 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% versus 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% versus 11.5%, respectively; time to response was 2.0 months in both arms (supplemental online Table 2). Grade 3–4 treatment-related adverse event (TRAE) rates were 27.5% for nivolumab and 32.0% for IC (supplemen-tal online 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 online Fig. 1). Median (range) duration of ther-apy was 1.9 (0–241) months for nivolumab and 1.9 (0–121) months for IC. Nivolumab continued to improve OS versus IC (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 online 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 nivo-lumab 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 versus 2.0 (1.9–4.6) months for IC. Median (range) duration of response was 9.7 (2.8–20.31) months versus 4.0 (1.51 to 8.51) 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 versus 36.0% for IC (supple-mental online Table 4). Select endocrine TRAEs were more fre-quent 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 versus IC, as were rates of high-grade TRAEs. Nivolumab is the only agent to significantly improve survival at primary analysis 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; how-ever, patients with platinum-refractory SCCHN were not included in the EXTREME trial. Patients eligible for Check-Mate 141, who were platinum-refractory due to progression within 6 months of treatment in the primary setting, are gen-erally not candidates for platinum-containing therapies such as EXTREME [7]. Their treatment options are limited to meth-otrexate, taxanes, or cetuximab—the IC options in the Check-Mate 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 ben-efits were observed with nivolumab versus IC in CheckMate 141 [8].

Conclusion

Although these data represent a small subgroup of patients, the results support the use of nivolumab as first-line ther-apy for patients with R/M SCCHN who progressed within 6 months of platinum-based therapy in the adjuvant or pri-mary setting. CheckMate 714 (NCT02823574) is an ongoing, randomized, double-blind, phase II study designed to evalu-ate the clinical benefit of adding anti–CTLA-4 targeted ther-apy (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 versus EXTREME (NCT02741570) [10].

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