

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

Received: 26 June 2021; Accepted: 30 November 2021.

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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

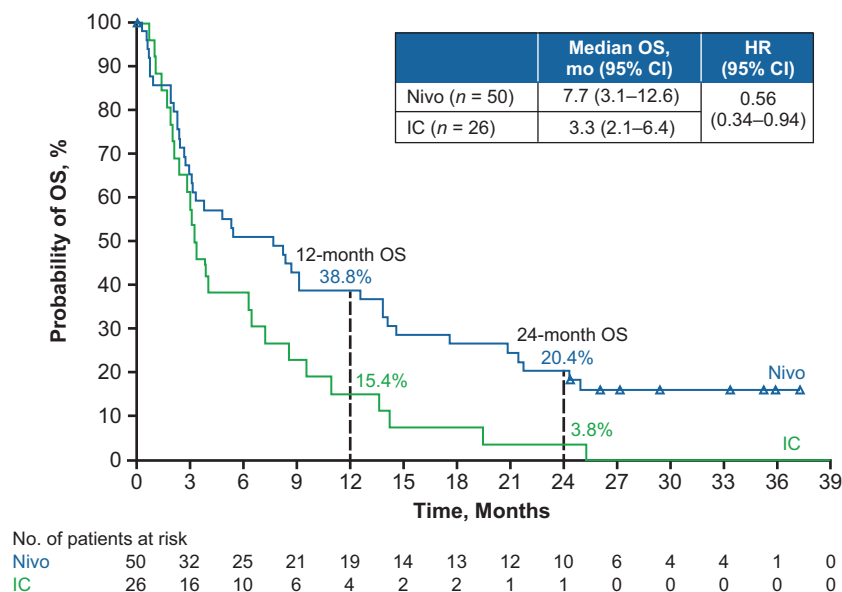


Figure 1. OS among patients randomized to nivolumab or IC as first-line treatment for recurrent or metastatic squamous cell carcinoma of the head and neck after progressing on or after platinum therapy (within 6 months) in the adjuvant or primary (ie, with radiation) setting for locally advanced disease.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

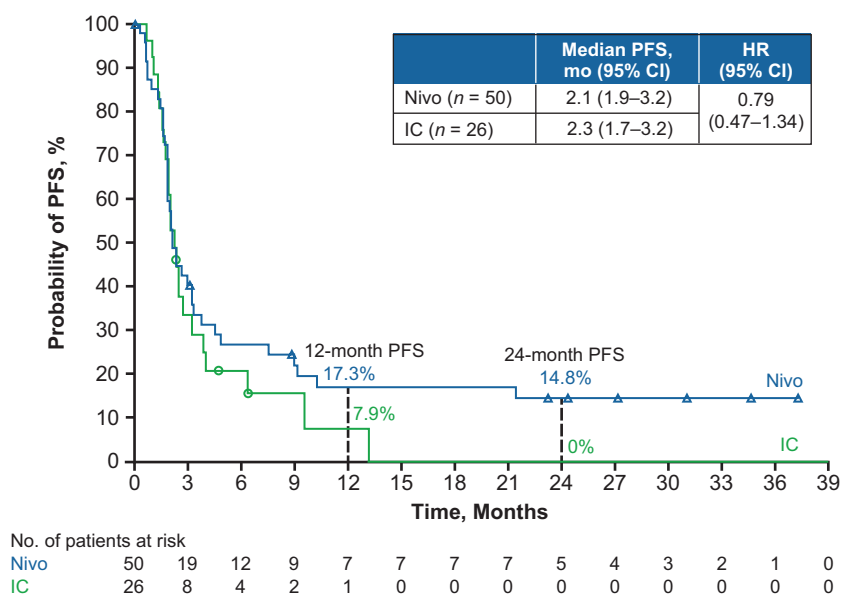


Figure 2. PFS among patients randomized to nivolumab or IC as first-line treatment for recurrent or metastatic squamous cell carcinoma of the head and neck after progressing on or after platinum therapy (within 6 months) in the adjuvant or primary (ie, with radiation) setting for locally advanced disease. 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.

Acknowledgments

The authors thank the patients and their families, as well as the clinical study teams, for making this study possible. This study was sponsored by Bristol Myers Squibb (Princeton, NJ, USA) and ONO Pharmaceutical Company Ltd. (Osaka, Japan). Professional medical writing assistance was provided by Meenakshi Subramanian, Ph.D., C.M.P.P., of Evidence Scientific Solutions, and was funded by Bristol Myers Squibb.

Conflict of Interest

Maura L. Gillison: Amgen Inc., Aspyrian Therapeutics, AstraZeneca Pharmaceuticals, Bayer Health Care Pharmaceuticals, Bicara, BioNTech, Bristol Myers Squibb, Celgene Corp, EMD Serono, Genocera Biosciences, Kura, Merck & Co, New Link Genetic Corporation, Roche, Roche Diagnostic, Shattuck Labs, TRM Oncology (Other—personal fees, during the conduct of the study), Amgen Inc., Aspyrian Therapeutics, AstraZeneca Pharmaceuticals, Bayer Health Care Pharmaceuticals, Bicara, BioNTech, Bristol Myers Squibb, Celgene Corp, EMD Serono, Genocera Biosciences, Kura, Merck & Co, New Link Genetic Corporation, Roche, Roche Diagnostic, Shattuck Labs, and TRM Oncology (Other—personal fees, outside the submitted work);

George Blumenschein, Jr.: Bristol Myers Squibb (RF and Other—personal fees, H—during the conduct of the study), Adaptimmune, Beigene, Exelixis, GlaxoSmithKline, Immatics, Immunocore, Incyte, Kite Pharma, MacroGenics, Regeneron, Repertoire Immune Medicines, Tmunit, Torque (RF), AbbVie, Adicet, Amgen, Ariad, Clovis Oncology, Johnson & Johnson/Janssen, Maverick Therapeutics and Virogin Biotech (Other—personal fees), AstraZeneca, Bayer, Bristol Myers Squibb, Celgene, Genentech, MedImmune, Merck, Novartis, Roche, and Xcovery (RF, Other—personal fees, outside the submitted work), Virogin (SAB, OI), Johnson & Johnson/Janssen (E, OI [immediate family member]); **Jerome Fayette:** AstraZeneca, BMS (Other, grants, personal fees and non-financial support), Merck Sharpe & Dohme (Other, personal fees and non-financial support), Merck, Innate (Other—personal fees, outside the submitted work); **Joel Guigay:** GSK (Other, grants) Merck KGaA-Serono (Other, grants and other fees), AstraZeneca, BMS, Innate Pharma (Other—other fees outside the submitted work); **A. Dimitrios Colevas:** reports no conflicts of interest; **Lisa Licitra:** Celgene International, Exelixis, Hoffmann-La Roche, IRX Therapeutics, Medpace, Pfizer (Other—grants), Amgen, Bayer, Doxa Pharma, GSK, Incyte Biosciences Italy, Ipsen, Nanobiotics Sa, Sobi (Other—personal fees), AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Debiopharm International SA, Eisai, Merck-Serono, Merck Sharpe & Dohme, Novartis, and Roche (Other—grants and personal fees, outside the submitted work); **Kevin J. Harrington:** Arch Oncology, Artios, AstraZeneca, Bristol Myers Squibb, Boehringer Ingelheim, Codiak, Idera Pharmaceuticals, ISA Therapeutics, Merck Serono, Mersana Therapeutics, Merck Sharpe & Dohme, Oncolys, Pfizer, and Replimune (C/A), AstraZeneca, Bristol Myers Squibb, Idera Pharmaceuticals, Merck Serono, Merck Sharpe & Dohme (H), AstraZeneca, Boehringer Ingelheim, Merck Sharpe & Dohme, Replimune (RF); **Stefan Kasper:** Bristol Myers Squibb (RF), AstraZeneca, Merck, Merck Sharp & Dohme (personal fees), Amgen, Bristol Myers Squibb, Roche, Lilly, Servier (personal fees outside the submitted work); **Everett E. Vokes:** AbbVie, Amgen, AstraZeneca, Biolumina, Bristol Myers Squibb, Celgene, Eli Lilly, EMD Serono, Genentech, Merck, Novartis, Regeneron (Other—personal fees, outside the submitted work); **Caroline Even:** Bristol Myers Squibb, Innate Pharma, Merck Serono, and Merck Sharpe & Dohme (Other—personal fees, outside the submitted work); **Francis Worden:** Bristol Myers Squibb, Lilly, Merck, Regeneron (Other—personal fees, outside the submitted work); **Nabil F. Saba:** Aduro, BioNTech, Blueprint, CUE, GSK, Kura, Merck, Pfizer, Vaccinex (C/A); **Lara Carmen Iglesias Docampo:** Bristol Myers Squibb, Bayer, Lilly, Merck, Merck Sharpe & Dohme, Roche (C/A), Eisai, Sanofi (Other—personal fees, outside the submitted work); **Robert Haddad:** AstraZeneca, Bristol Myers Squibb, Genentech, GSK, Merck, Pfizer (Other—personal fees, during the conduct of the study), AstraZeneca, Bristol Myers Squibb, Genentech, GSK, Merck, Pfizer (Other—personal fees, outside the submitted work); **Tamara Rordorf:** Bristol Myers Squibb, Merck Sharp & Dohme (C/A); **Naomi Kiyota:** AstraZeneca, Bristol Meyers Squibb, Chugai Pharmaceutical, Ono Pharmaceutical, Pfizer, Rakuten Medical (RF, during the conduct of the study), AstraZeneca, Bayer, Bristol Myers Squibb, Eisai, Merck Biopharma, Merck Sharp & Dohme, Ono Pharmaceutical (H); **Makoto Tahara:** Bristol Myers Squibb, Ono Pharmaceutical (Other—grants and personal fees, during the conduct of the study, Amgen, Celgene, and LOXO

(Other—personal fees), AstraZeneca, Bayer, Eisai, Merck Serono, Merck Sharp & Dohme, Novartis, Rakuten Medical (Other—grants and personal fees, outside the submitted work); **Vijayvel Jayaprakash:** Bristol Myers Squibb (E during manuscript development, OI); **Li Wei:** Bristol Myers Squibb (E, OI); **Robert L. Ferris:** Aduro Biotech, Bicara, EMD Serono, GlaxoSmithKline, Iovance Biotherapeutics, MacroGenics, Nanobiotix, Numab Therapeutics AG, Oncorus, Pfizer, PPD, Regeneron Pharmaceuticals, Torque Therapeutics (Other—personal fees), Tesaro (RF), AstraZeneca/MedImmune, Bristol Myers Squibb, Merck (Other—grants and personal fees), Novasenta (Other—grants, personal fees and other fees); Ono Pharmaceutical (Other, personal fees and other fees, outside the submitted work).

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

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.

References

- Ferris RL, Blumenschein G Jr, Fayette J, et al. Nivolumab for recurrent squamous-cell carcinoma of the head and neck. *N Engl J Med*. 2016;375(19):1856-1867.
- Harrington KJ, Ferris RL, Blumenschein G Jr, et al. Nivolumab versus standard, single-agent therapy of investigator's choice in recurrent or metastatic squamous cell carcinoma of the head and neck (CheckMate 141): health-related quality-of-life results from a randomised, phase 3 trial. *Lancet Oncol*. 2017;18(8):1104-1115.
- Ferris RL, Blumenschein G Jr, Fayette J, et al. 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. *Oral Oncol*. 2018;81:45-51. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6563923/>
- Gillison ML, Blumenschein G Jr, Fayette J, et al. CheckMate 141: 1-year update and subgroup analysis of nivolumab as first-line therapy in patients with recurrent/metastatic head and neck cancer. *Oncologist*. 2018;23(9):1079-1082.
- Le X, Ferrarotto R, Wise-Draper T, Gillison M. Evolving role of immunotherapy in recurrent metastatic head and neck cancer. *J Natl Compr Canc Netw*. 2020;18(7):899-906.
- Vermorken JB, Mesia R, Rivera F, et al. Platinum-based chemotherapy plus cetuximab in head and neck cancer. *N Engl J Med*. 2008;359(11):1116-1127.

7. Guigay J, Aupérin A, Fayette J, et al.; GORTEC; AIO; TTCC, and UniCancer Head and Neck groups. Cetuximab, docetaxel, and cisplatin versus platinum, fluorouracil, and cetuximab as first-line treatment in patients with recurrent or metastatic head and neck squamous-cell carcinoma (GORTEC 2014-01 TPExtreme): a multicentre, open-label, randomised, phase 2 trial. *Lancet Oncol.* 2021;22(4):463-475.
8. Burtneß B, Harrington KJ, Greil R, et al.; KEYNOTE-048 Investigators. Pembrolizumab alone or with chemotherapy versus cetuximab with chemotherapy for recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-048): a randomised, open-label, phase 3 study. *Lancet.* 2019;394(10212):1915-1928.
9. Argiris A, Harrington KJ, Tahara M, et al. Nivolumab (N) + ipilimumab (I) vs EXTREME as first-line (1L) treatment (tx) for recurrent/metastatic squamous cell carcinoma of the head and neck (R/M SCCHN): final results of CheckMate 651 (LBA36). *Ann Oncol.* 2021;32(suppl_5):S1283-S1346.