Nivolumab Treatment Beyond RECIST-Defined Progression in Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck in CheckMate 141: A Subgroup Analysis of a Randomized Phase 3 Clinical Trial

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BACKGROUND: Response patterns with immune checkpoint inhibitors may be different from those with chemotherapy. Therefore, assessment of response to immunotherapy with the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1, could result in premature treatment termination. The randomized, open-label, phase 3 CheckMate 141 trial (NCT02105636), which evaluated nivolumab in recurrent/metastatic squamous cell carcinoma of the head and neck after platinum therapy, allowed treatment beyond first RECIST-defined progression (TBP) according to protocol-specified criteria. METHODS: In CheckMate 141, patients with RECIST-defined progression who had a stable performance status and demonstrated clinical benefit without rapid disease progression were permitted to receive TBP with nivolumab at 3 mg/kg every 2 weeks until further progression, which was defined as an additional ≥10% increase in tumor volume. This post hoc analysis evaluated outcomes for patients who received TBP with nivolumab. RESULTS: Of 240 patients randomized to nivolumab, 146 experienced RECIST-defined progression. Sixty-two of these patients received TBP, and 84 discontinued treatment (no TBP). Among the 60 TBP patients evaluable for response, 15 (25%) had no change in their tumor burden, and 15 (25%) had reductions in target lesion size; 3 patients (5%) had reductions >30%. The median overall survival among TBP patients was 12.7 months (95% confidence interval, 9.7-14.6 months). No new safety signals were observed with TBP. Exploratory analyses of immune cell biomarkers suggested a potential relationship with initial and TBP responses. CONCLUSIONS: Tumor burden reduction was noted in a proportion of patients who received TBP with nivolumab in CheckMate 141. Additional research is warranted to identify factors predictive of a TBP benefit in this population. Cancer 2019;125:3208-3218.

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KEYWORDS: immunotherapy, nivolumab, phase 3 clinical trials, squamous cell carcinoma of the head and neck.

INTRODUCTION

Nivolumab demonstrated a significant overall survival (OS) benefit and a favorable safety profile compared with investigator’s choice of therapy in the primary analysis of CheckMate 141 (NCT02105636) in patients with recurrent/metastatic squamous cell carcinoma of the head and neck (SCCHN) who had experienced tumor progression or recurrence within 6 months of platinum-based chemotherapy in the adjuvant, primary (ie, with radiation), recurrent, or metastatic setting. Survival and safety benefits were maintained at the 1- and 2-year follow-up.

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In CheckMate 141, the tumor response was assessed with the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1. The RECIST guidelines, which were developed for assessment of chemotherapy-treated tumors, assume that early tumor growth indicates progressive disease. With immunotherapy, however, some patients exhibit distinct response patterns, including apparent increases in tumor size due to immune and inflammatory cell infiltration, and/or delayed clinical response. Therefore, RECIST assessment of a tumor response to immunotherapy could result in an incorrect diagnosis of disease progression and premature termination of treatment. In CheckMate 141, treatment beyond first RECIST-defined progression (TBP) with nivolumab was permitted at the discretion of investigators, according to protocol-defined criteria, for patients who were likely to benefit from continued treatment; results from this analysis are reported.

MATERIALS AND METHODS

Patients and Study Design

The full study methodology of the randomized, open-label, phase 3 CheckMate 141 study has been described previously. Patients were randomized 2:1 to receive intravenous nivolumab at 3 mg/kg every 2 weeks or the investigator’s choice, which consisted of intravenous methotrexate (40-60 mg/m² weekly), docetaxel (30-40 mg/m² weekly), or cetuximab (400 mg/m² once and then 250 mg/m² weekly). Treatment was continued until the occurrence of unacceptable toxicity or disease progression except in patients assigned to the nivolumab treatment arm who met the protocol-defined criteria for TBP. The primary endpoint of the study was OS; patients were followed up for survival during treatment and every 3 months after discontinuation. The objective response rate (ORR), defined as the proportion of patients with a best overall response of confirmed complete response or partial response according to RECIST, version 1.1, was a secondary endpoint. The tumor response was assessed by investigators every 6 weeks beginning week 9. The association of immune cell phenotypes with a clinical response was assessed as an exploratory endpoint. Safety was monitored throughout treatment and for 100 days after the administration of the last dose.

CheckMate 141 was approved by institutional review boards at all participating sites. Patients provided informed consent before enrollment.

Treatment Beyond First RECIST-Defined Progression

Per protocol, TBP was permitted at the discretion of investigators in consultation with the study monitors if a patient demonstrated clinical benefit without rapid disease progression, tolerated nivolumab, maintained a stable performance status, and provided informed consent. Clinical benefit was assessed according to whether the patient was clinically deteriorating and unlikely to receive further benefit from continued treatment. TBP was not permitted if it would cause a delay in an intervention to prevent serious complications from disease progression. Treatment could continue until evidence of further progression, which was defined as an additional ≥10% increase in the tumor volume from the time of first progression in all target lesions and new measurable lesions.

Patients in the nivolumab arm who received their last dose of treatment after RECIST-defined progression were included in the TBP group; patients whose last dose of nivolumab occurred before RECIST-defined
progression were included in the no treatment beyond first RECIST-defined progression (NTBP) group.

**Biomarkers**

Blood samples were collected from patients at baseline and on day 43 of treatment in Vacutainer CPT cell preparation tubes with sodium heparin and were centrifuged according to the manufacturer’s recommended procedure to isolate peripheral blood lymphocytes. The cells were washed with phosphate-buffered saline or Roswell Park Memorial Institute 1640 medium and then resuspended in a freezing medium of fetal bovine serum plus 10% dimethyl sulfoxide. The cells were immediately frozen at −70 °C for up to 72 hours before they were moved to long-term storage in liquid nitrogen. Frozen peripheral blood lymphocyte (PBL) samples were

### TABLE 1. Characteristics of Patients With RECIST-Defined Progression Treated With Nivolumab

| Characteristic                          | TBP Patients (n = 62) | TBP Patients Who Experienced Reductions in Target Lesion Size (n = 15) | NTBP Patients (n = 84) |
|----------------------------------------|-----------------------|------------------------------------------------------------------------|------------------------|
| **Baseline Characteristics**           |                       |                                                                        |                        |
| Age, median (range), y                 | 59.0 (29-78)          | 58.0 (29-67)                                                           | 61.0 (30-83)           |
| Male, No. (%)                          | 52 (84)               | 14 (93)                                                                | 71 (85)                |
| Primary site of disease, No. (%)       |                       |                                                                        |                        |
| Oral cavity                            | 26 (42)               | 3 (20)                                                                 | 33 (39)                |
| Pharynx                                | 28 (46)               | 9 (60)                                                                 | 36 (43)                |
| Larynx                                 | 8 (13)                | 3 (20)                                                                 | 13 (15)                |
| Other\(^a\)                            | 0                     | 0                                                                      | 2 (2)                  |
| Disease sites (primary and metastatic) per patient, No. (%)\(^ab\) |                       |                                                                        |                        |
| 1                                      | 20 (32)               | 6 (40)                                                                 | 24 (29)                |
| 2                                      | 27 (44)               | 5 (33)                                                                 | 26 (31)                |
| 3                                      | 8 (13)                | 2 (13)                                                                 | 27 (32)                |
| ≥4                                     | 7 (11)                | 2 (13)                                                                 | 7 (8)                  |
| ECOG PS, No. (%)                       |                       |                                                                        |                        |
| 0                                      | 21 (34)               | 8 (53)                                                                 | 21 (25)                |
| 1                                      | 19 (31)               | 4 (27)                                                                 | 17 (20)                |
| Not reported                            | 22 (35)               | 3 (20)                                                                 | 46 (55)                |
| HPV status, No. (%)\(^d\)              |                       |                                                                        |                        |
| Positive                               | 21 (34)               | 8 (53)                                                                 | 21 (25)                |
| Negative                               | 19 (31)               | 4 (27)                                                                 | 17 (20)                |
| Unknown/not reported                   | 22 (35)               | 3 (20)                                                                 | 46 (55)                |
| PD-L1 expression, No. (%)              |                       |                                                                        |                        |
| ≥1%                                    | 27 (44)               | 5 (33)                                                                 | 28 (33)                |
| <1%                                    | 17 (27)               | 6 (40)                                                                 | 30 (36)                |
| Not quantifiable at baseline           | 18 (29)               | 4 (27)                                                                 | 26 (31)                |
| Lactate dehydrogenase                  |                       |                                                                        |                        |
| Median (range), U/L                    | 210.0 (97-1799)\(^a\) | 188.0 (114-919)                                                        | 252.5 (94-4138)        |
| Normal, No. (%)                        | 47 (77)\(^a\)         | 10 (67)                                                                | 62 (74)                |
| High, No. (%)                          | 14 (23)\(^a\)         | 5 (33)                                                                 | 22 (26)                |
| Tobacco use, No. (%)                   |                       |                                                                        |                        |
| Current/former                         | 49 (79)               | 13 (87)                                                                | 71 (85)                |
| Never                                  | 12 (19)               | 2 (13)                                                                 | 10 (12)                |
| Unknown                                | 1 (2)                 | 0                                                                      | 3 (4)                  |
| **Characteristics at First RECIST-Defined Progression** |                       |                                                                        |                        |
| ECOG PS, No. (%)                       |                       |                                                                        |                        |
| 0                                      | 22 (35)               | 11 (13)                                                                | 32 (38)                |
| 1                                      | 40 (65)               | 32 (38)                                                                | 32 (38)                |
| 2                                      | 0                     | 7 (8)                                                                  | 7 (8)                  |
| Not reported                            | 0                     | 34 (40)                                                                | 34 (40)                |
| Type of RECIST progression, No. (%)    |                       |                                                                        |                        |
| Target lesion                          | 38 (61)               | 47 (56)                                                                | 47 (56)                |
| New lesion                             | 3 (5)                 | 4 (5)                                                                  | 4 (5)                  |
| Both                                   | 21 (34)               | 33 (39)                                                                | 33 (39)                |

Abbreviations: ECOG, Eastern Cooperative Oncology Group; HPV, human papillomavirus; NTBP, no treatment beyond first RECIST-defined progression; PD-L1, programmed death ligand 1; PS, performance status; RECIST, Response Evaluation Criteria in Solid Tumors; TBP, treatment beyond first RECIST-defined progression.

\(^a\)Other includes patients with a tumor in more than 1 of the 3 categories (ie, larynx, oral cavity, and pharynx).

\(^b\)Patients could have had lesions at more than 1 site.

\(^c\)Both target and non-target lesions are included.

\(^d\)The HPV status was assessed with p16 immunohistochemical testing and was required only for patients with oropharyngeal cancer.

\(^e\)Data were available for 61 patients; percentages were calculated with 61 as the denominator.
shipped to the analyzing laboratory in liquid nitrogen vapor shippers.

At the laboratory, vials were thawed in a water bath at 37°C for 1 minute; then, the sample from each vial was transferred into a 15-mL conical tube containing warm Roswell Park Memorial Institute 1640 medium, washed twice by sequential centrifugation, resuspended in 5 mL of phosphate-buffered saline and stained with viability dye Zombie Aqua (BioLegend, San Diego, California) according to the manufacturer’s protocol, and then stained for multicolor flow cytometry. Samples were stained for CD8^+ T cells with the following mouse anti-human monoclonal antibodies: TCRαβ AF700, CD8 APC-Cy7, CCR7-BV650, and CD45RA-BV711. Samples were stained for regulatory T cells with the following mouse anti-human antibodies: CD4-AF700, CD25-BV650, CD127-BV785, and FOXP3-PerCPCy5.5. All antibodies were purchased from BD Bioscience (San Jose, California). Mouse anti-human PD-1-APC (clone MIH4; eBioscience), cyto -

| TABLE 2. Efficacy in the TBP and NTBP Patient Groups Before First RECIST-Defined Progression |
|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
| Best overall response, No. (%) | TBP Group (n = 62) | NTBP Group (n = 84) |
| Partial response | 10 (16) | 5 (6) |
| Stable disease | 20 (32) | 17 (20) |
| Progressive disease | 32 (52) | 62 (74) |
| Objective response rate, No. (%) | 95% CI | 8-28 | 2-13 |
| Maximum reduction in target lesion, median (range), % | 7 (−86 to 129) | 23 (−55 to 162) |
| Time to response, median (range), mo | 2.1 (1.8-4.8) | 2.0 (1.8-5.1) |
| Duration of response, median (range), mo | 6.4 (2.8-9.7) | 5.5 (4.0-6.9) |

Abbreviations: CI, confidence interval; NTBP, no treatment beyond first RECIST-defined progression; RECIST, Response Evaluation Criteria in Solid Tumors; TBP, treatment beyond first RECIST-defined progression.

with a generalization of the Brookmeyer and Crowley method. Two-sided 95% CIs for ORRs were computed with the Clopper and Pearson method. A 2-way analysis of variance with Šidák’s multiple comparisons test correction was used to descriptively analyze the PBL biomarker data. The database lock for efficacy and safety was September 2016, which represented a minimum follow-up of 11.8 months. The database lock for biomarkers was August 2017.

The Bristol-Myers Squibb policy on data sharing can be found at https://www.bms.com/researchers-and-partners/independent-research/data-sharing-request-process.html.

RESULTS

Patients

Of 240 patients randomized to nivolumab, 146 (61%) experienced RECIST-defined progression (Fig. 1). Sixty-two of these patients (42%) met the criteria for TBP and continued to receive nivolumab treatment; 84 (58%) discontinued treatment (NTBP). Among the remaining 94 of 240 patients (39%), 4 did not receive nivolumab, 11 were continuing treatment as of the data cutoff, and the rest discontinued treatment primarily because of either a lack of confirmation of disease progression or adverse events.

Patient characteristics at baseline and at RECIST-defined progression were summarized in Table 1. Overall, the baseline characteristics were similar between patients in the 2 groups, although a larger percentage of TBP patients had a baseline Eastern Cooperative Oncology Group performance status of 0. The most common
sites of metastases at baseline were similar between the TBP group (lung, 53%; lymph nodes, 48%) and the NTBP group (lung, 52%; lymph nodes, 54%). In both groups, RECIST-defined progression in the majority of patients was due to an increase in the size of target lesions either with (TBP, 34%; NTBP, 39%) or without the development of new lesions (TBP, 61%; NTBP, 56%; Table 1).

Efficacy
The ORR before RECIST-defined progression was higher in the TBP group (16%) than the NTBP group (6%; Table 2). Of the 62 patients who underwent TBP with nivolumab, 60 were evaluable for response; 15 (25%) had no change in their tumor burden, and 15 (25%) had reductions in the target lesion size. Three patients (5%) had a reduction >30% (Fig. 2). For 9 of the 15 patients with reductions in the target lesion size (60%), the pharynx was the primary site of disease (Table 1). Five of the 15 patients with tumor reductions after TBP had previously experienced a >20% increase in the target lesion size at RECIST-defined progression, and only 1 had a preprogression best overall response of partial response. The median time to tumor burden reduction among the 15 patients with reductions after RECIST-defined progression was 3.9 months (range, 3.1-15.8), and the median duration of tumor reduction was 3.0 months (range, <0.1-15.4+). Reductions were observed in patients with human papillomavirus (HPV)-positive and HPV-negative tumors as well as those with tumor programmed death ligand 1 (PD-L1) expression ≥1% or <1%.

Among patients receiving TBP with nivolumab, the median OS was 12.7 months (95% CI, 9.7-14.6 months; Fig. 3A); the estimated OS rates for these patients at 12 and 18 months were 52% and 30%, respectively. In the overall intent-to-treat population (including patients in the TBP and NTBP groups as well as those who did not experience RECIST-defined progression), the median OS for nivolumab-treated patients was 7.7 months (95% CI, 5.7-8.8 months; Fig. 3B). In a landmark analysis, the median OS starting week 6 after RECIST-defined progression was 8.4 months (95% CI, 6.6-10.8 months) in the TBP group and 3.8 months (95% CI, 2.1-5.3 months) in the NTBP group (Fig. 4).

Biomarkers
Peripheral blood lymphocyte samples from baseline and day 43 of treatment were available for 14 TBP patients; 3 of these patients were TBP responders, and 11 were TBP nonresponders. In addition, samples were available for 26 patients assessed with RECIST (16 responders and 10 nonresponders). Across all immune cell phenotypes, there were no significant differences in baseline biomarker levels between RECIST and TBP responders. Differences in the levels of total CD8+ T cells, PD-1+ CD8+ effector T cells, and exhausted PD-1+ TIM-3+ CD8+ effector T cells as well as PD-1+ regulatory T cells and CTLA-4+...
regulatory T cells were noted between responders and nonresponders (RECIST and/or TBP) at baseline and/or day 43, although not all differences were significant (Fig. 5A,B). There was a wide variation in the levels of CTLA-4+ CD8+ effector T cells. Among TBP responders (n = 3), there was a significant reduction in PD-1+ regulatory T cell levels on day 43 in comparison with baseline; this difference was not noted in nonresponders (n = 11). In contrast, the CD8+ T cell compartment did not show any significant differences between TBP responders and nonresponders after nivolumab treatment.

**Safety**

Treatment-related adverse events (TRAEs) and select TRAEs are summarized in Table 3. When adjusted for duration of therapy exposure, the incidence of TRAEs, with the exception of skin and subcutaneous tissue disorders, was lower in the TBP group than the NTBP group (Table 4).
DISCUSSION
In this post hoc analysis of CheckMate 141, tumor burden reduction was noted in 15 of 60 patients (25%) who underwent TBP with nivolumab; 3 patients (5%) experienced a reduction >30%. In the context of all patients randomized to receive nivolumab in the trial, this translates to an efficacy benefit of treatment beyond progression in 1.3% (3 of 240). The median OS was 12.7 months for patients receiving TBP with nivolumab and 7.7 months in the overall intent-to-treat population. In a landmark analysis, the median OS starting week 6 after RECIST-defined progression was 8.4 months for the TBP group and 3.8 months for the NTBP group. No new safety signals were noted with TBP. Efficacy benefits after TBP with nivolumab have also been reported for melanoma, non–small cell lung cancer, and renal cell carcinoma.

In CheckMate 141, the ORR before RECIST-defined progression was higher in the TBP group than
the NTBP group; this was expected on the basis of the protocol-defined requirement that patients demonstrate an investigator-assessed clinical benefit to be eligible for TBP. The characteristics of the TBP and NTBP patients were similar at baseline except for a better Eastern Cooperative Oncology Group performance status in the TBP group. These findings are similar to those reported in a recent pooled TBP analysis conducted by the US Food and Drug Administration in patients with melanoma. Among the 15 TBP patients in this analysis who achieved
any reduction in the target lesion size after progression, 8 (53%) had HPV-positive cancers.

It is important to note that although interesting, the small patient numbers in our study preclude us from drawing definitive conclusions about patient characteristics predictive of clinical benefit from treatment with nivolumab beyond RECIST-defined progression. The criteria for TBP used in this analysis are similar to those used for TBP with nivolumab in reports for other tumors. Nonetheless, a key limitation of the analysis is

**TABLE 3. TRAEs Reported in ≥10% of Patients and Select TRAEs**

|                      | TBP Patients (n = 62) | NTBP Patients (n = 84) |
|----------------------|-----------------------|------------------------|
|                      | Any Grade | Grade 3-4 | Any Grade | Grade 3-4 |
| Any TRAE, No. (%)    | 48 (77)    | 9 (15)    | 51 (61)    | 12 (14)    |
| Fatigue              | 10 (16)    | 1 (2)     | 17 (20)    | 2 (2)      |
| Rash                 | 10 (16)    | 0         | 6 (7)      | 0          |
| Pruritus             | 9 (15)     | 0         | 3 (4)      | 0          |
| Anemia               | 3 (5)      | 1 (2)     | 9 (11)     | 2 (2)      |
| Decreased appetite   | 3 (5)      | 0         | 10 (12)    | 0          |
| Select TRAEs, No. (%)|           |           |           |            |
| Skin                 | 19 (31)    | 0         | 10 (12)    | 0          |
| Endocrine            | 8 (13)     | 0         | 8 (10)     | 0          |
| Gastrointestinal     | 6 (10)     | 0         | 8 (10)     | 1 (1)      |
| Hepatic              | 3 (5)      | 0         | 2 (2)      | 1 (1)      |
| Pulmonary            | 2 (3)      | 0         | 3 (4)      | 1 (1)      |
| Hypersensitivity/infusion reactions | 1 (2) | 0 | 1 (1) | 0 |
| Renal                | 1 (2)      | 0         | 0          | 0          |

Abbreviations: NTBP, no treatment beyond first RECIST-defined progression; RECIST, Response Evaluation Criteria in Solid Tumors; TBP, treatment beyond first RECIST-defined progression; TRAE, treatment-related adverse event.

**TABLE 4. Exposure-Adjusted Incidence of Treatment-Related Adverse Events in ≥10% of Patients**

|                      | TBP Patients (n = 62) | NTBP Patients (n = 84) |
|----------------------|-----------------------|------------------------|
|                      | Events, No. | Rate per 100 P-Y | Events, No. | Rate per 100 P-Y |
| Total events         | 184         | 489               | 150         | 618               |
| Skin and subcutaneous tissue disorders | 43 | 114               | 13 | 54               |
| Rash                 | 14          | 37                | 6          | 25                |
| Pruritus             | 9           | 24                | 4          | 16                |
| General disorders and administration site conditions | 26 | 69               | 29 | 119               |
| Fatigue              | 10          | 27                | 18         | 74                |
| Metabolism and nutrition disorders | 17 | 45                | 19 | 78                |
| Decreased appetite   | 5           | 13                | 11         | 45                |
| Blood and lymphatic system disorders | 5 | 13               | 12 | 49                |
| Anemia               | 3           | 8                 | 9          | 37                |

Abbreviations: NTBP, no treatment beyond first RECIST-defined progression; P-Y, person-years of exposure; RECIST, Response Evaluation Criteria in Solid Tumors; TBP, treatment beyond first RECIST-defined progression.

*37.6 P-Y.

Currently, no treatment beyond first RECIST-defined progression.

**Figure 5.** (A) Levels of CD8⁺ effector T cells among RECIST-defined responders, RECIST-defined nonresponders, responders to treatment beyond first RECIST-defined progression, and nonresponders to treatment beyond first RECIST-defined progression. (B) Levels of regulatory T cells among the RECIST-defined responders, RECIST-defined nonresponders, responders to treatment beyond first RECIST-defined progression, and nonresponders to treatment beyond first RECIST-defined progression. Dark blue bars represent baseline values; light blue bars represent day 43 values. Horizontal lines indicate medians, boxes indicate interquartile ranges, and whiskers indicate minimum and maximum values. CD8⁺ effector T cells were considered to be exhausted CD8⁺ effector T cells. Regulatory T cells were defined as CD4⁺CD25hiCD127loFoxP3⁺. *P < .05; **P < .01; ***P < .001. CR indicates complete response; CTLA-4, cytotoxic T lymphocyte antigen 4; PD, progressive disease; PD-1, programmed cell death 1; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; TBPNR, treatment beyond first RECIST-defined progression with stable or increased tumor lesion after progression; TBPR, treatment beyond first RECIST-defined progression with reduction in tumor lesion after progression; TIM-3, T cell immunoglobulin and mucin-domain containing-3.
that the selection of patients for TBP with nivolumab was based on an assessment of clinical benefit by investigators and not on clearly defined, validated factors. Therefore, it is possible that the results of this analysis are confounded by selection bias because patients with more favorable disease characteristics and better prognosis were probably selected for inclusion in the TBP group. Despite the limitations, our analysis underscores the potential benefits of TBP with nivolumab and the need for identifying factors predictive of TBP benefit in this patient population.

Exploratory analyses of cellular immune biomarkers suggested a potential relationship with initial and TBP responses. TBP with nivolumab appeared to diminish immunosuppressive signals from PD-1+ regulatory T cells. It should be noted, however, that the sample sizes were small, and this research should be considered hypothesis-generating. Comprehensive analyses involving larger patient populations in prospective clinical trials are warranted to fully understand these effects. In this study, on-treatment PBL samples were collected on day 43 of treatment, a prespecified time point for the collection of on-treatment PBL samples. The timing was based on the assumption that 6 weeks was adequate to evaluate changes in frequencies in the adaptive immune cell compartment in comparison with baseline values and to assess the expression of markers of activation or exhaustion. However, the timing of the PBL sample collection was independent of the timing of the tumor response; this could have resulted in a large variability in on-treatment biomarker levels.

Because of the limitations of RECIST in accurately characterizing tumor responses to immunotherapy, guidelines such as immune-related response criteria (irRC),5 immune-related RECIST (irRECIST) and immune-modified RECIST (imRECIST),16-19 and modified RECIST, version 1.1, for immune-based therapeutics (iRECIST)20 have been developed. The goal of these guidelines is 2-fold: to ensure that treatment is not prematurely terminated for patients with tumor responses to immunotherapy that are different from responses typical of cytotoxic chemotherapy and to ensure that treatment is discontinued in a timely manner in patients with true disease progression because this can affect potential benefits from subsequent lines of treatment.20

In summary, patients with RECIST-defined progression who do not experience rapid disease progression, have a stable performance status, and are able to tolerate treatment may derive a clinical benefit from TBP with nivolumab for recurrent/metastatic SCCHN. Our results underscore the importance of conducting prospective trials aimed at evaluating the eligibility and appropriate selection of patients who may derive a benefit from TBP. Additional research is also needed to determine whether a response to TBP can be predicted on the basis of immunologic factors or patient clinical characteristics. Our results indicate that continued TBP with nivolumab is not associated with new safety concerns.

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