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ORIGINAL ARTICLE

Efficacy and safety of pembrolizumab monotherapy in patients with advanced thyroid cancer in the phase 2 KEYNOTE-158 study

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Abstract

Background: The authors report results from the thyroid carcinoma cohort of the multicohort phase 2 KEYNOTE-158 study (NCT02628067), which evaluated pembrolizumab monotherapy in patients with previously treated cancers.

Methods: Eligible patients had histologically and/or cytologically confirmed papillary or follicular thyroid carcinoma, failure of or intolerance to prior therapy, and measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. Patients received pembrolizumab (200 mg) every 3 weeks for up to 35 cycles. The primary end point was objective response rate (ORR) per RECIST v1.1 by independent central review.

Results: A total of 103 patients were enrolled and received pembrolizumab. Median duration from first dose to data cutoff (October 5, 2020) was 49.4 (range, 43.9–54.9) months. ORR was 6.8% (95% confidence interval [CI], 2.8%–13.5%), and median duration of response was 18.4 (range, 4.2–47.2+) months. ORR was 8.7% (95% CI, 2.4%–20.8%) among patients with programmed cell death ligand 1 (PD-L1) combined positive score (CPS) ≥1 (n = 46) and 5.7% (95% CI, 1.2%–15.7%) among patients with PD-L1 CPS <1 (n = 53). Median overall survival and progression-free survival were 34.5 (95% CI, 21.2 to not reached) and 4.2 (95% CI, 3.9–6.2) months, respectively. Treatment-related adverse events occurred in 69.9% of patients (grade 3–5, 14.6%).

Conclusions: Pembrolizumab demonstrated manageable toxicity and durable antitumor activity in a small subset of patients with advanced thyroid cancer. These

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results provide evidence of modest antitumor activity in this setting regardless of tumor PD-L1 expression. Future studies evaluating immune checkpoint inhibitors in patients with differentiated thyroid cancer should focus on biomarker-driven patient selection or combination of immune checkpoint inhibitors with other agents, in order to achieve higher response rates than observed in this study.

KEYWORDS
immunotherapy, pembrolizumab, programmed cell death 1 ligand 1, programmed cell death 1 receptor, thyroid neoplasms

INTRODUCTION

Most diagnoses of thyroid cancer are of differentiated papillary (90%) or follicular carcinomas (5%) and are typically managed successfully with resection and radioactive iodine therapy.[1] However, for disease that is refractory to radioiodine, recurrent, or metastatic, alternative treatment approaches are necessary.[1,2] For patients with recurrent or metastatic differentiated thyroid cancer that is unresectable and/or has become refractory to radioactive iodine therapy, the current National Comprehensive Cancer Network and European Society for Medical Oncology guidelines recommend systemic therapy with lenvatinib or sorafenib.[1,2] Lenvatinib and sorafenib have demonstrated response rates of 65% and 31%, respectively, and appear to attenuate disease progression and extend progression-free survival (PFS).[3–5] However, it is uncertain whether they provide an overall survival (OS) benefit, and many patients develop resistance within 1 to 2 years after beginning treatment.[3,5,6]

The microenvironment of differentiated thyroid cancer is enriched with nearly all types of immune cells.[7] Whereas certain immune cells might slow tumor progression in thyroid cancer, many are a source of proinflammatory and protumorigenic cytokines and chemokines.[7,8] This process of tumor immune activation includes an increase in T cells and regulatory T cells that express immune checkpoints such as programmed cell death protein 1 (PD-1), which has been associated with more aggressive disease characteristics such as extranodal invasion.[7,9] Notably, increased expression of programmed cell death ligand 1 (PD-L1) has been associated with disease progression (PD).[10–12]

Given the potential role of the immune system and inflammatory pathways in the development and progression of differentiated thyroid cancer, there has been interest in evaluating immune checkpoint inhibitor therapy in this setting.[13] The phase 1b KEYNOTE-028 study was the first clinical study to evaluate the anti–PD-1 monoclonal antibody pembrolizumab in patients with differentiated thyroid cancer.[13,14] In KEYNOTE-028, which enrolled patients with previously treated advanced PD-L1–positive disease, the objective response rate (ORR) was 9% for the cohort of patients with thyroid cancer, and the safety profile was manageable, with treatment-related adverse events (AEs) occurring in 82% of patients.[14] In the phase 2 KEYNOTE-158 study of pembrolizumab monotherapy, patients with advanced solid tumors were enrolled regardless of PD-L1 status. Results from the cohort of patients with advanced thyroid carcinomas enrolled in KEYNOTE-158 are reported here.

MATERIALS AND METHODS

Study design and conduct

KEYNOTE-158 is an ongoing single-arm, multicenter, multicohort, open-label study of pembrolizumab monotherapy. Cohort I includes patients with thyroid carcinoma.

Patients provided written informed consent to participate. The study was conducted in accordance with the Declaration of Helsinki, the International Council for Harmonisation Good Clinical Practice guidelines, and all applicable local and national laws. The institutional review board at each study site approved the protocol, all protocol amendments, and informed consent forms before the study began.

Eligibility criteria

Adults (≥18 years old) were eligible to enroll if they had histologically or cytologically confirmed thyroid carcinoma (papillary or follicular subtypes) with progression on or intolerance to at least one prior line of standard treatment for metastatic and/or unresectable disease. Eligible patients had measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 with confirmation by independent central radiologic review; Eastern Cooperative Oncology Group performance status of 0 or 1; life expectancy of at least 3 months; and adequate hematologic, renal, hepatic, and coagulation function. All enrolled patients were required to provide a tumor sample for biomarker analysis. Per the protocol, serum thyroglobulin was not assessed during the study. Patients were permitted to enroll regardless of tumor PD-L1 status. Patients were ineligible to participate if they had any of the following: active autoimmune disease that required systemic treatment within the previous 2 years; diagnosis of immunodeficiency; receipt of systemic steroid therapy or other immunosuppressive therapy within 7 days before beginning pembrolizumab treatment; other known malignancy within 2 years before enrolling (exceptions were curatively treated basal cell carcinoma, squamous cell

carcinoma, and curatively resected in situ cancers); central nervous system metastasis or carcinomatous meningitis; known glioblastoma multiforme of the brain stem; prior or current noninfectious pneumonitis that required steroids; or history or current evidence of any other condition, therapy, or laboratory abnormality that might interfere with the patient's participation in the study or confound study results.

Treatment

Pembrolizumab (200 mg) was administered as a 30-minute intravenous infusion once every 3 weeks for 35 cycles (approximately 2 years) or until confirmed radiologic PD, progression or recurrence of any malignancy or occurrence of another malignancy requiring treatment, unacceptable toxicity, intercurrent illness that prevented treatment administration, investigator decision, patient withdrawal, or loss to follow-up. Patients who had a complete response (CR) were allowed to stop pembrolizumab treatment after administration of at least eight cycles of treatment.

Assessments

PD-L1 status was assessed centrally using the PD-L1 IHC 22C3 pharmDx assay (Agilent Technologies, Carpinteria, California). Combined positive score (CPS) was calculated as the number of PD-L1–staining cells (tumor cells, lymphocytes, and macrophages) divided by the total number of viable tumor cells and multiplied by 100. Tumors with CPS of at least 1 were considered to be PD-L1 positive; tumors with a CPS less than 1 were considered to be PD-L1 negative.

Tumor imaging using computed tomography or magnetic resonance imaging was performed at baseline, every 9 weeks for the first 12 months, and every 12 weeks thereafter. Imaging assessments were performed until confirmed PD or until patients began a new anticancer treatment, withdrew consent, or died.

The occurrence of AEs was monitored at all study visits through the safety follow-up visit (30 days after treatment discontinuation [90 days for serious AEs]) and efficacy follow-up visits (every 12 weeks after treatment discontinuation). AEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0.

End points

The primary efficacy end point was ORR per RECIST version 1.1 as determined by independent central radiologic review. ORR was defined as the proportion of patients who attained CR or partial response (PR). Secondary efficacy end points were duration of response (DOR), PFS, OS, safety, and tolerability. DOR was defined as the time from first documented evidence of CR or PR per RECIST version 1.1 as assessed by independent central review to the time of PD or death due to any cause. PFS was defined as the time from allocation to PD per RECIST version 1.1 as assessed by independent central review. OS was defined as the time from allocation to the date of death.

Statistical analysis

The study was planned to enroll approximately 100 patients in cohort I regardless of primary tumor biomarker status. Efficacy and safety analyses included all patients who received at least one dose of pembrolizumab. Patients with missing data were treated as nonresponders. The primary end point of ORR was analyzed for both the overall cohort and for subgroups according to PD-L1 status. Analyses of ORR used point estimates and Clopper-Pearson 95% confidence intervals (CIs). DOR, PFS, and OS were estimated using the Kaplan–Meier method. Statistical analyses were performed using SAS version 9.4 (SAS Institute, Inc, Cary, North Carolina).

RESULTS

Patient disposition

Overall, 103 patients were enrolled at 43 sites in 18 countries between February 15, 2016, and January 11, 2017. Sixteen patients (15.5%) completed treatment, and 87 patients (84.5%) discontinued treatment due to disease progression (n = 67 [65.0%]; including radiographic and clinical progression), AEs (n = 12 [11.7%]), patient withdrawal (n = 6 [5.8%]), physician decision (n = 1 [1.0%]), or loss to follow-up (n = 1 [1.0%]). The median time from first dose of pembrolizumab to data cutoff (October 5, 2020) was 49.4 (range, 43.9–54.9) months.

Patients had a median age of 62.0 years and nearly all had stage IV disease (98.1%; Table 1). A majority (62.1%) had received at least two prior lines of systemic therapy.

ORR

In the overall cohort, ORR was 6.8% (95% CI, 2.8–13.5). Among the seven patients with an objective response, two had a CR and five had a PR (Table 2). Median time to response was 2.1 months (range, 1.3–10.3), and median DOR was 18.4 months (range, 4.2–47.2+) (Figure 1). Sixty-nine (67.0%) patients experienced disease control, which was defined as a CR, PR, or stable disease. Among the 95 PD-L1–evaluable patients with at least one postbaseline tumor assessment, 41 (43.2%) had a reduction in tumor size relative to baseline and 10 (10.5%) had at least a 30% reduction in tumor size (Figure 2). The ORR was 8.7% (95% CI, 2.4–20.8) among the 46 patients with PD-L1–positive disease (CR, n = 2; PR, n = 2) and 5.7% (95% CI, 1.2–15.7) among the 53 patients with PD-L1–negative disease (PR, n = 3).

PFS and OS

Overall, 96 (93.2%) patients experienced a PFS event by the data cutoff date (Figure 3A). The median PFS was 4.2 months (95% CI, 3.9–6.2), and the estimated 12- and 24-month PFS rates were 28.0% and 6.8%, respectively. Fifty-seven (55.3%) patients died, and the median OS was 34.5 months (95% CI, 21.2–not reached) (Figure 3B). The estimated 12-, 24-, 36-, and 48-month OS rates were 81.6%, 59.0%, 48.2%, and 45.9%, respectively.

TABLE 1 Baseline demographics and disease characteristics

	Patients, $N = 103$
Age, median (range), years	62.0 (27–85)
Women, No. (%)	55 (53.4)
ECOG performance status, No. (%)[a]	
0	52 (50.5)
1	50 (48.5)
No. of prior lines of systemic therapy, No. (%)	
0 or adjuvant/neoadjuvant/definitive	7 (6.8)
1	32 (31.1)
2	24 (23.3)
≥3	40 (38.8)
Prior radiation therapy, No. (%)[b]	55 (53.4)
PD-L1 status, No. (%)	
PD-L1–positive	46 (44.7)
PD-L1–negative	53 (51.5)
Not evaluable	4 (3.9)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; PD-L1, programmed cell death ligand 1.

[a]One patient had ECOG performance status 2 at baseline.

[b]Patients who received palliative radiotherapy.

Safety

Treatment-related AEs occurred in 72 (69.9%) patients (Table 3). The most frequently occurring treatment-related AEs were fatigue (19.4%), pruritus (14.6%), and rash (14.6%). Thirteen (12.6%) patients had at least one grade 3 or 4 treatment-related AE, and two (1.9%) patients died due to a grade 5 treatment-related AE (arterial hemorrhage, $n = 1$; malignant neoplasm progression, $n = 1$). The death due to arterial hemorrhage was considered by the investigator to be caused by a reduction in pressure on arterial structures following tumor regression. The death due to malignant neoplasm progression involved tumor hyperprogression that the investigator considered to be related to study treatment. Ten (9.7%) patients discontinued pembrolizumab due to a treatment-related AE.

Immune-mediated AEs and infusion reactions occurred in 16 (15.5%) patients. The most common immune-mediated AEs of any grade were colitis (3.9%) and hyperthyroidism (2.9%); 3.9% of patients experienced an infusion reaction. Grade 3 immune-mediated AEs occurred in five patients (4.9%; adrenal insufficiency, colitis, hepatitis, pneumonitis, type 1 diabetes mellitus, 1.0% each); no grade 4 or 5 immune-mediated AEs or grade 3–5 infusion reactions were reported.

DISCUSSION

A small subset of patients with advanced thyroid carcinoma attained an objective response during pembrolizumab treatment in the

TABLE 2 Antitumor activity per RECIST version 1.1 by independent central review

	All patients, $N = 103$[a]	Patients with PD-L1–positive tumors,[a] $n = 46$	Patients with PD-L1–negative tumors, $n = 53$
ORR, % (95% CI)[b]	6.8 (2.8–13.5)	8.7 (2.4–20.8)	5.7 (1.2–15.7)
Best overall response, No. (%)			
CR	2 (1.9)	2 (4.3)	0
PR	5 (4.9)	2 (4.3)	3 (5.7)
SD	62 (60.2)	27 (58.7)	31 (58.5)
Non-CR/non-PD[c]	1 (1.0)	0	1 (1.9)
PD	32 (31.1)	14 (30.4)	18 (34.0)
No assessment[d]	1 (1.0)	1 (2.2)	0
Disease control (CR + PR + SD), No. (%)	69 (67.0)	31 (67.4)	34 (64.2)

Abbreviations: CR, complete response; ORR, objective response rate; PD, progressive disease; PD-L1, programmed cell death ligand 1; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

[a]Four patients were not evaluable for PD-L1 status.

[b]Based on binomial exact confidence interval method.

[c]Persistence of ≥1 nontarget lesion.

[d]"No assessment" includes patients who had a baseline assessment but no postbaseline assessment by the data cutoff date (October 5, 2020).

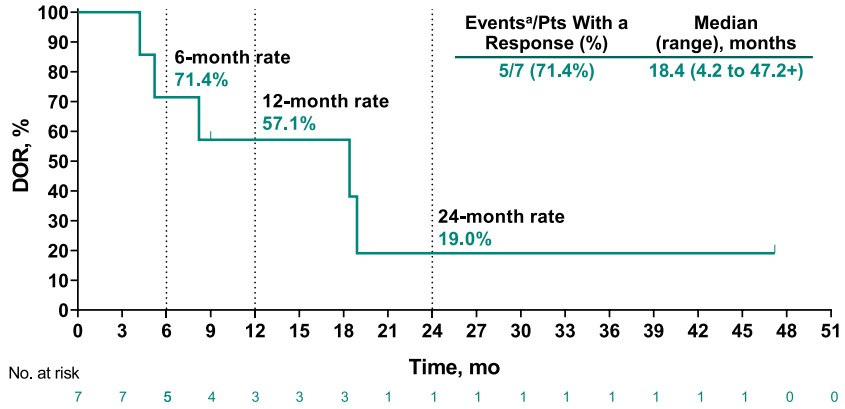

FIGURE 1 DOR per RECIST version 1.1 by independent central review. Response includes patients with confirmed CR or PR. Data cutoff date, October 5, 2020. CR, complete response; DOR, duration of response; PR, partial response; pts, patients; RECIST, Response Evaluation Criteria in Solid Tumors. [a]Events were defined as disease progression or death.

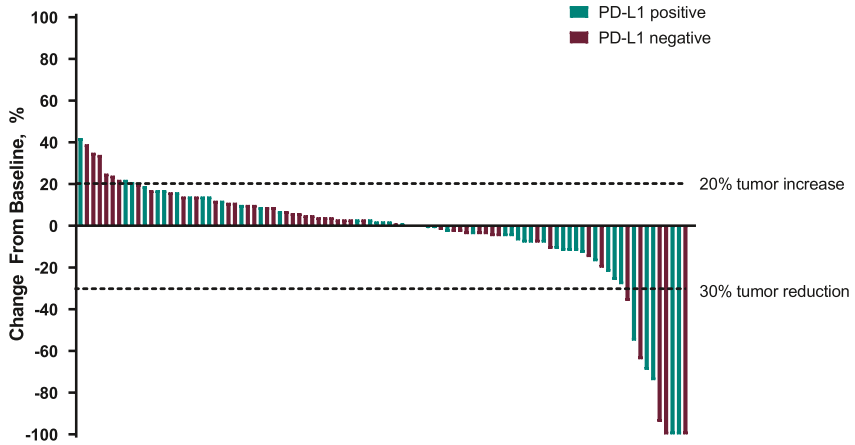

FIGURE 2 Best percentage change from baseline in target lesion size per RECIST version 1.1 by independent central review for PD-L1–evaluable patients with ≥1 postbaseline assessment ($N = 95$). Percentage changes from baseline >100% are presented as 100%. In the two patients with CR, tumor histology was papillary carcinoma and poorly differentiated follicular carcinoma. In the five patients with PR, all were papillary carcinoma or adenocarcinoma. Data cutoff date, October 5, 2020. PD-L1, programmed cell death ligand 1; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors. [a]Of three nonresponders with >30% tumor reduction from baseline, two patients experienced unconfirmed PR, and one patient experienced a new lesion.

KEYNOTE-158 study. Responses were observed in seven of 103 (6.8%) of patients regardless of tumor PD-L1 status and were durable. After a median 49.5-month follow-up, two of seven patients maintained a response. Approximately half of enrolled patients were alive at 3 years. Despite the single-arm study design, the results provide a large data set that suggests evidence of antitumor activity for a small subgroup of patients with differentiated thyroid cancer who received pembrolizumab. However, the biological features that define the population of responders are uncertain. Our results demonstrated modest antitumor activity of pembrolizumab against both PD-L1–positive and PD-L1–negative differentiated thyroid carcinomas. This analysis represents the largest study conducted to date of checkpoint inhibitor monotherapy in patients with thyroid carcinoma. The cohort with thyroid cancer in KEYNOTE-028 was smaller ($N = 22$).[14] Caution is warranted for any between-study comparisons, particularly given the differences between populations in terms of disease characteristics; for example, in KEYNOTE-028, all patients had PD-L1–positive tumors and approximately one-third had not received prior systemic treatment. Despite these caveats, the 9% ORR for patients with PD-L1–positive disease in the current analysis is similar to the 9% ORR reported in KEYNOTE-028.

In this study, pembrolizumab had a manageable safety profile that was consistent with previous observations in patients with advanced solid tumors who received pembrolizumab monotherapy.[14–21] In the current analysis, the overall rate of treatment-related AEs was somewhat lower than the rate reported for patients with PD-L1–positive thyroid cancer in KEYNOTE-028 (70% and 82%, respectively). Given that thyroidectomy is a standard therapy for thyroid cancer, the lower incidence of immune-mediated hyperthyroidism and hypothyroidism (which have previously been associated with pembrolizumab monotherapy) than

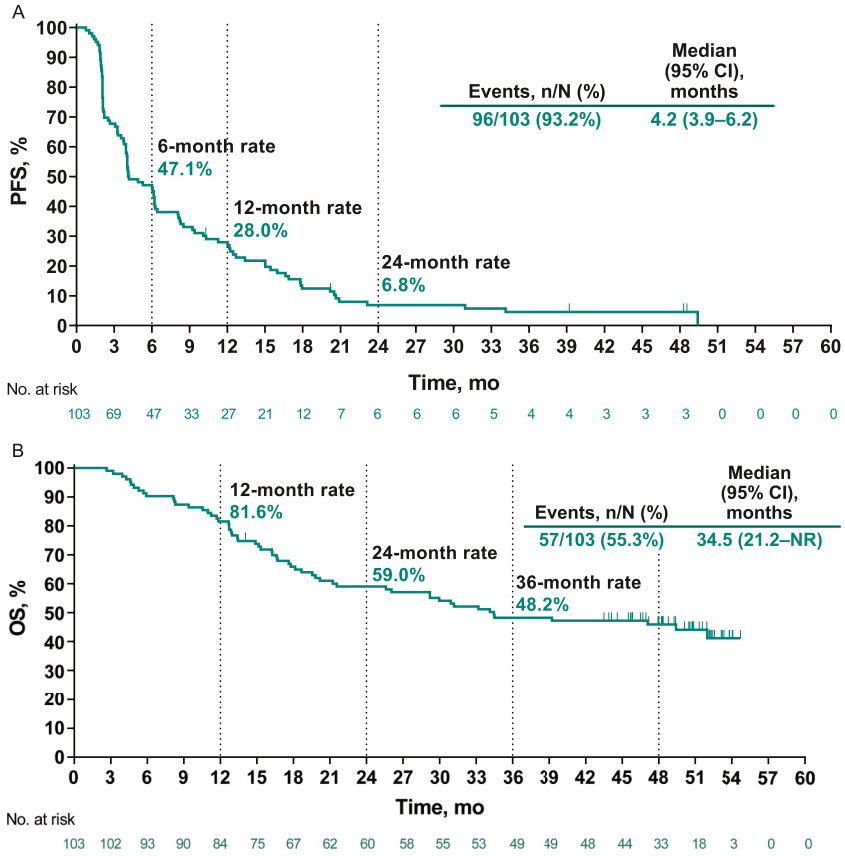

FIGURE 3 (A) PFS per RECIST version 1.1 by independent central review and (B) OS. Data cutoff date, October 5, 2020. NR, not reached; OS, overall survival; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors.

reported for other cohorts in KEYNOTE-158 was not unanticipated.[1,2,15,18] Few patients in our analysis discontinued pembrolizumab due to a treatment-related AE. Two deaths were considered by investigators to be related to treatment. These included one death that was considered to be caused by complications following tumor regression and one death due to tumor hyperprogression.

Responses were observed in both patients with PD-L1–positive and PD-L1–negative advanced thyroid carcinomas. However, although responses appeared to occur regardless of PD-L1 status, these data must be interpreted with caution given the very small number of patients with an objective response in this study. Other biomarkers have been evaluated among patients enrolled in the KEYNOTE-158 study. In particular, tumor-agnostic analyses from the KEYNOTE-158 study showed that high levels of microsatellite instability/mismatch repair–deficiency and high tumor mutational burden were associated with response during pembrolizumab treatment; these analyses included patients from the thyroid cohort.[16,18]

The clinical evidence for immune checkpoint inhibitor therapy in patients with differentiated thyroid cancer is only beginning to emerge.[13,22] To our knowledge, only one other study is evaluating monotherapy with a checkpoint inhibitor (spartalizumab) for patients with advanced differentiated thyroid cancer (NCT04802876), and no studies other than KEYNOTE-028 and KEYNOTE-158 have reported results. However, results have been reported from two phase 2 studies that evaluated checkpoint inhibition as part of a combination regimen for patients with differentiated thyroid cancer. In one of the studies, the combination of nivolumab (anti–PD-1) and ipilimumab (anti–cytotoxic T-lymphocyte–associated protein 4 [anti–CTLA-4]) elicited an ORR of 9.4%.[23] In the other study, patients treated with the combination of pembrolizumab and lenvatinib had a 62% ORR (all PRs).[24] Ongoing studies of combination regimens with checkpoint inhibitors include combinations of anti–PD-1 and anti–CTLA-4 therapy (NCT02834013); anti–PD-1 therapy and a CEACAM1 inhibitor (NCT04731467); anti–PD-1 therapy plus MEK and BRAF inhibitors (NCT04061980 and NCT04544111); and anti–PD-1 therapy combined with small-molecule vascular endothelial growth factor receptor inhibitors, with or without ipilimumab (NCT03914300, NCT04514484, and NCT03170960).

ORR was selected as the primary end point for this single-arm study. Some evidence has suggested that, in phase 2 studies evaluating immune checkpoint inhibitors, ORR may not correlate with PFS and OS and underestimate clinical benefit.[25,26] Prior studies of targeted therapies in patients with thyroid cancer have reported 2-year OS rates of approximately 60%.[3,4,27] In this context, the observed 2-year OS rate of 59.0% and 3-year OS rate of 48.2% in this study are suggestive of clinical benefit with pembrolizumab, particularly given that 39% of patients in the current study had received three or more

TABLE 3 Adverse Events

	Patients, No. (%), $N = 103$	
Patients with any treatment-related AE	72 (69.9)	
Grade 3	12 (11.7)	
Grade 4[a]	1 (1.0)	
Grade 5[b]	2 (1.9)	
Led to treatment discontinuation	10 (9.7)	
	Any grade	**Grades 3–5[a,b]**
Treatment-related AEs occurring in ≥5 patients		
Fatigue	20 (19.4)	2 (1.9)
Pruritus	15 (14.6)	0
Rash	15 (14.6)	0
Arthralgia	8 (7.8)	1 (1.0)
Asthenia	7 (6.8)	0
Decreased appetite	5 (4.9)	0
Diarrhea	5 (4.9)	0
Immune-mediated AEs and infusion reactions occurring in ≥1 patient[c]	16 (15.5)	5 (4.9)[d]
Colitis	4 (3.9)	1 (1.0)
Infusion reactions	4 (3.9)	0
Hyperthyroidism	3 (2.9)	0
Hepatitis	2 (1.9)	1 (1.0)
Hypothyroidism	2 (1.9)	0
Adrenal insufficiency	1 (1.0)	1 (1.0)
Myelitis	1 (1.0)	0
Pneumonitis	1 (1.0)	1 (1.0)
Type 1 diabetes mellitus	1 (1.0)	1 (1.0)
Immune-mediated AEs or infusion reactions leading to treatment discontinuation[c]	3 (2.9)	

Note: Data cutoff date, October 5, 2020.

Abbreviation: AEs, adverse events.

[a]One patient experienced grade 4 events of acute motor axonal neuropathy and subdural hematoma.

[b]Arterial hemorrhage ($n = 1$) and malignant neoplasm progression ($n = 1$).

[c]Events were based on a list of terms (including related terms) specified at the time of analysis and were included regardless of attribution to study treatment or immune relatedness by the investigator.

[d]No grade 4 AEs, fatal immune-mediated AEs, or infusion reactions occurred.

lines of prior therapy. However, it is difficult to evaluate the magnitude of any such benefit given the absence of a comparator arm. Assessment of ORR per RECIST version 1.1 provides a conservative estimate of antitumor activity in this study.

In conclusion, these results show modest antitumor activity with pembrolizumab monotherapy regardless of PD-L1 status. Among the small group of patients who experienced a response, those responses were durable, and the safety profile was consistent with what was previously reported with pembrolizumab. These findings build on an earlier, smaller study of pembrolizumab monotherapy in a patient population with PD-L1–positive disease.[14] Future studies evaluating immune checkpoint inhibitors in patients with differentiated thyroid cancer should focus on biomarker-driven patient selection or combination of immune checkpoint inhibitors with other agents to achieve higher response rates than observed in this study.

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CONFLICTS OF INTEREST

Do-Youn Oh reports consultant and/or advisory board fees from ASLAN, AstraZeneca, Basilea, Bayer, BeiGene, Bristol-Myers Squibb/Celgene, Genentech/Roche, Halozyme, Merck Serono, Novartis, Taiho, Turning Point, Yuhan, and Zymeworks; research grants from Array, AstraZeneca, BeiGene, Eli Lilly, Handok, Novartis, Servier, and Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA. Alain Algazi reports research support, advisory board member, consultant, shareholder, and honoraria recipient from OncoSec; advisory board member and stock shareholder for Valitor Biosciences and Sensei; advisory board member and honorarium recipient from Regeneron and Array; research support from Acerta, Amgen, AstraZeneca, Bristol Myers Squibb, Dynavax, Genentech, Idera, Incyte, ISA, LOXO, Merck, Novartis, Sensei, and Tessa; consultant for, honorarium recipient, and shareholder for Onchilles; consultant and honorarium recipient for Venn and IAG; and DSMB member for Worldwide Clinical Trials. Jaume Capdevila reports consultant and/or advisory board fees from Bayer, Eisai, Ipsen, Exelixis, ITM, Adacap, Novartis, Pfizer, Merck Serono, Lilly, Hudchinson Medipharma, and Esteve and research grants from Eisai, AstraZeneca, Ipsen, Roche, and Adacap. Federico Longo reports speaker and/or advisory role fees from MSD, Bristol Myers Squibb, Lilly, Roche, Merck Serono, Amgen, Servier, and Bayer. Wilson Miller, Jr reports grants or contracts to the institution from Merck, Canadian Institutes of Health Research, Cancer Research Society, Terry Fox Research Institute, Samuel Waxman Cancer Research Foundation, and Canadian Cancer Society Research Institute; consulting fees from Merck, Bristol Myers Squibb, Roche, GlaxoSmithKline, Novartis, Amgen, Mylan, EMD Serono, and Sanofi; honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from McGill University, JGH, Bristol Myers Squibb, Merck, Roche, GlaxoSmithKline, Novartis, Amgen, Mylan, EMD Serono, and Sanofi; and support to the institution for clinical trial participation from Bristol Myers Squibb, Novartis, GlaxoSmithKline, Roche, AstraZeneca, Methylgene, MedImmune, Bayer, Amgen, Merck, Incyte, Pfizer, Sanofi, Array, MiMic, Ocellaris Pharma, Astellas, Alkermes, Exelixis, Array, VelosBio, and Genentech. Jerry Tan Chun Bing reports consultant and/or advisory fees from Amgen/Zuellig Pharma, Boehringer Ingelheim, Hi-Eisai, Merck Sharp & Dohme, Pfizer, and Roche. Carlos Eduardo Bonilla reports serving on advisory boards for Amgen, Janssen, Bristol, Merck Serono, Pfizer, Roche, Bayer, AstraZeneca, and Merck Sharp & Dohme; acting as an investigator in clinical trials from Bristol, Merck Sharp & Dohme, and Novartis; and receiving sponsorship to attend oncology meetings from Bristol, Amgen, Janssen, Merck Sharp & Dohme, Roche, and Merck Serono. Hyun Cheol Chung reports funding to the institution from Merck Sharp & Dohme, Lilly, GlaxoSmithKline, Merck Serono, Bristol Myers Squibb/Ono, Taiho, Amgen, Beigene, Incyte, Zymework; advisory boards for Taiho, Celltrion, Merck Sharp & Dohme, Lilly, Bristol Myers Squibb, Merck Serono, Gloria, Beigene, Amgen, and Zymework; and honoraria for lectures from Merck Serono and Lilly. Tormod K. Guren reports honoraria to the institution from Pierre Fabre. Chia-Chi Lin serves on advisory boards for AbbVie, Blueprint Medicines, Boehringer Ingelheim, Bristol Myers Squibb, Daiichi Sankyo, Merck KGaA, Novartis, and PharmaEngine; honoraria from Eli Lilly, Novartis, and Roche; and travel support from BeiGene, Daiichi Sankyo, and Eli Lilly. Daniel Motola-Kuba reports consultant and/or advisory board fees from AstraZeneca, Bayer, Bristol Myers Squibb, Roche, Merck Sharp & Dohme, and Novartis. Manisha Shah reports research funding from Merck and Eli Lilly. Julien Hadoux reports serving on advisory boards for IPSEN, Lilly, Roche, Pharma Mar, and AAA and research support from Novartis. Fan Jin owns stock in Merck & Co., Inc.,

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DATA AVAILABILITY STATEMENT

Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA (MSD) is committed to providing qualified scientific researchers access to anonymized data and clinical study reports from the company's clinical trials for the purpose of conducting legitimate scientific research. MSD is also obligated to protect the rights and privacy of trial participants and, as such, has a procedure in place for evaluating and fulfilling requests for sharing company clinical trial data with qualified external scientific researchers. The MSD data sharing website (available at: http://engagezone.msd.com/ds_documentation.php) outlines the process and requirements for submitting a data request. Applications will be promptly assessed for completeness and policy compliance. Feasible requests will be reviewed by a committee of MSD subject matter experts to assess the scientific validity of the request and the qualifications of the requestors. In line with data privacy legislation, submitters of approved requests must enter into a standard data-sharing agreement with MSD before data access is granted. Data will be made available for request after product approval in the United States and European Union or after product development is discontinued. There are circumstances that may prevent MSD from sharing requested data, including country or region-specific regulations. If the request is declined, it will be communicated to the investigator. Access to genetic or exploratory biomarker data requires a detailed, hypothesis-driven statistical analysis plan that is collaboratively developed by the requestor and MSD subject matter experts; after approval of the statistical analysis plan and execution of a data-sharing agreement, MSD will either perform the proposed analyses and share the results with the requestor or will construct biomarker covariates and add them to a file with clinical data that is uploaded to an analysis portal so that the requestor can perform the proposed analyses.

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