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Pembrolizumab for the Treatment of Advanced Salivary Gland Carcinoma

Findings of the Phase 1b KEYNOTE-028 Study

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Objectives: Treatment options for patients with unresectable or metastatic salivary gland carcinoma (SGC) are limited. Safety and efficacy of pembrolizumab for SGC expressing programmed death ligand 1 (PD-L1) were explored.

Materials and Methods: A cohort of patients with advanced, PD-L1-positive SGC was enrolled in the nonrandomized, multicohort, phase Ib trial of pembrolizumab in patients with PD-L1-positive advanced solid tumors (KEYNOTE-028; NCT02054806). Key inclusion criteria included recurrent or metastatic disease, failure of prior systemic therapy, and PD-L1 expression on $\geq 1\%$ of tumor or stroma cells (per a prototype immunohistochemistry assay). Patients received pembrolizumab 10 mg/kg every 2 weeks for ≥ 2 years or until confirmed disease progression or unacceptable toxicity. Primary end point was objective response rate per Response Evaluation Criteria in Solid Tumors version 1.1 by investigator review.

Results: Twenty-six patients with PD-L1-positive SGC were enrolled and treated; median age was 57 years, 88% were men, and 74% had received prior therapy for recurrent/metastatic disease. Confirmed objective response rate after median follow-up of 20 months was 12% (95% confidence interval, 2%-30%), with 3 patients achieving partial response; there were no complete responses. Median duration of response was 4 months (range, 4 to 21 mo). Treatment-related adverse events occurred in 22 patients (85%), resulting in discontinuation in 2 patients and death in 1 (interstitial lung disease); those occurring in $\geq 15\%$ of patients were diarrhea, decreased appetite, pruritus, and fatigue.

Conclusions: Pembrolizumab demonstrated promising antitumor activity and a manageable safety profile in patients with advanced, PD-L1-positive SGC.

Key Words: salivary gland cancer, immunotherapy, pembrolizumab, anti-PD-1

(*Am J Clin Oncol* 2018;41:1083–1088)

Salivary gland carcinomas (SGCs) are rare, accounting for <5% of head and neck cancers, and are histologically diverse, with 24 different types identified.[1,2] SGCs are generally slow growing and characterized by a prolonged clinical course, frequent local recurrence, and latent distant metastases.[3]

Treatment options for patients with unresectable or metastatic (advanced) SGC are limited to chemotherapy or

participation in a clinical trial.[2,4] Response rates to single agents (cisplatin, carboplatin, paclitaxel, docetaxel, 5-fluorouracil, methotrexate, capecitabine, cetuximab, gemcitabine, or vinorelbine) range from 15% to 35%, whereas rates are usually double with combination regimens (cisplatin or carboplatin plus 5-fluorouracil with cetuximab, cisplatin or carboplatin plus a taxane, cisplatin with cetuximab, or cisplatin with 5-fluorouracil).[2]

Molecular aberrations are expressed differentially among SGC subtypes and have been identified as potential therapeutic targets.[1] These include altered expressions of c-kit tyrosine kinase receptor,[5] epidermal growth factor receptor,[6] c-ErbB2 (HER2/neu),[7] and hormone receptors.[8]

The programmed death 1 (PD-1) receptor is expressed on activated T cells and inhibits effector T-cell function upon binding of its ligands, PD-L1 and PD-L2.[9] Upregulation of the PD-1 pathway, which is involved in the induction and maintenance of peripheral immune tolerance, leads to suppression of immune response in many tumors.[10] In an analysis of 217 surgically resected SGC specimens, high PD-L1 expression was reported in high-grade SGC subtypes previously shown to be associated with aggressive behavior (eg, salivary duct carcinoma and squamous cell carcinoma).[11] An association between PD-L1 positivity and inferior disease-free survival was also observed.[11] In addition, PD-L2 expression has been found in several tumor types, including adenoid cystic carcinoma, one of the most lethal SGCs.[12,13]

Pembrolizumab is a fully humanized immunoglobulin G4/κ anti-PD-1 monoclonal antibody. Pembrolizumab has demonstrated robust antitumor activity and a favorable safety profile in multiple tumor types and is currently approved in >60 countries for 1 or more advanced malignancies, including in the United States for recurrent or metastatic head and neck squamous cell carcinoma that progressed on or after platinum-containing chemotherapy.[14–16] The safety and antitumor activity of pembrolizumab in patients with advanced, PD-L1-positive SGC enrolled in the phase 1b, multicohort KEYNOTE-028 trial (NCT02054806) are reported here.

PATIENTS AND METHODS

Study Design and Patients

KEYNOTE-028 is an ongoing multicenter, open-label, phase 1b trial of pembrolizumab in patients with PD-L1-positive advanced solid tumors. Patient eligibility criteria for the SGC cohort included age 18 years and older; histologically or cytologically documented locally advanced or metastatic SGC of any subtype (except sarcomas or mesenchymal tumors) for which standard therapy was ineffective, does not exist, or is not considered appropriate; PD-L1-positive disease; measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1; Eastern Cooperative Oncology Group performance status (ECOG PS) 0-1; and adequate organ function.

Exclusion criteria included a diagnosis of immunodeficiency or received systemic steroid therapy within 7 days, prior monoclonal antibody anticancer therapy within 4 weeks, and chemotherapy, targeted small-molecule therapy, or radiation therapy within 2 weeks of first pembrolizumab dose; active autoimmune disease; interstitial lung disease; known additional progressing malignancy; and active brain metastases. Previous treatment with an immune checkpoint inhibitor was not allowed. The study protocol was approved by institutional review boards or ethics committees of all participating sites. All enrolled patients provided written informed consent. This article describes off-label use of pembrolizumab for the treatment of PD-L1-positive SGC.

Treatment and Assessments

Pembrolizumab 10 mg/kg was administered through intravenous infusion every 2 weeks for 24 months or until confirmed disease progression (PD), unacceptable adverse events (AEs), or investigator/patient decision to withdraw. Treatment was withheld in cases of unacceptable toxicity but

TABLE 1. Baseline Demographics and Clinical Characteristics

Characteristics (n [%])*	N = 26
Age, median (range) (y)	57 (23-72)
Male	23 (88)
Race	
White	12 (46)
Asian	9 (35)
Black or African American	2 (8)
Not specified	3 (12)
ECOG performance status	
0	7 (27)
1	19 (73)
Baseline SGC histology	
Adenocarcinoma	10 (38)
Mucoepidermoid	3 (12)
Undifferentiated	2 (8)
Squamous cell	2 (8)
Adenoid cystic	2 (8)
Other†	7 (27)
Metastatic stage	
MX	2 (8)
M0	4 (15)
M1	17 (65)
M1C	1 (4)
Unknown	2 (8)
Prior adjuvant or neoadjuvant systemic therapy	8 (31)
Prior lines of therapy for advanced disease‡	
0	3 (12)
1	9 (35)
2	4 (15)
3	2 (8)
4	2 (8)
≥5	2 (8)
Previous therapies received by ≥2 patients§	
Taxane‖ + a platinum¶	15 (58)
A platinum¶ + other#	16 (62)
Fluorouracil ± a platinum¶ ± other**	5 (19)
Trastuzumab ± a platinum¶ ± a taxane‖	3 (12)
Vinorelbine ± a platinum¶	2 (8)
Cetuximab monotherapy	3 (12)
Doxorubicin monotherapy	3 (12)
Capecitabine ± trastuzumab††	3 (12)
Tegafur ± uracil	2 (8)
Goserelin acetate monotherapy	2 (8)

*Unless stated otherwise.

†Poorly differentiated, high-grade serous, adenosquamous, salivary duct, carcinoid, dedifferentiated acinic, and epithelial with basaloid features; n = 1 for each.

‡Unknown for 4 patients.

§Patients could be counted more than once because they may have received >1 prior therapy listed.

‖Paclitaxel or docetaxel.

¶Carboplatin or cisplatin.

#Cyclophosphamide, fluorouracil, amifostine, or vinorelbine tartrate.

**Bevacizumab, docetaxel, cetuximab, gemcitabine.

††Capecitabine, vinorelbine tartrate.

ECOG indicates Eastern Cooperative Oncology Group; SGC, salivary gland carcinoma; ±, with or without.

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could be resumed after resolution of toxicity to grade 0/1 within 12 weeks of the last infusion; otherwise, treatment was discontinued. Response was assessed by computed tomography or magnetic resonance imaging every 8 weeks for the first 6 months and every 12 weeks thereafter. Clinically stable patients with radiographic progression who had no further increase in tumor dimensions on subsequent scans could continue treatment at the investigator's discretion. Patients were considered clinically stable if they met the following criteria: absence of signs and symptoms indicating disease progression, no decrease in ECOG PS, absence of rapid disease progression, and absence of a progressive tumor at a critical anatomic site that would necessitate urgent alternative medical intervention. AEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 and monitored throughout and for 30 days after treatment discontinuation (90 days for serious AEs). Immune-mediated AEs were defined as events with potentially drug-related immunologic causes that were consistent with an immune phenomenon, regardless of attribution by the investigator.

Tumor PD-L1 positivity was determined at a central laboratory using formalin-fixed archived or newly obtained biopsy samples and a prototype immunohistochemical assay (QualTek Molecular Laboratories, Goleta, CA),[17] based on the 22C3 antibody (Merck & Co. Inc., Kenilworth, NJ). Positivity was defined as membranous staining on ≥1% modified proportion score or interface pattern, as described elsewhere.[17,18]

End Points

The primary efficacy end point was objective response rate (ORR) by investigator review, defined as the proportion of patients having complete response (CR) or partial response (PR) per RECIST version 1.1. Secondary end points were duration of response (time from first RECIST response to PD), progression-free survival (PFS; time from enrollment to first documented PD or death from any cause, whichever occurred first), overall survival (OS), and safety and tolerability.

TABLE 2. Treatment-related Adverse Events, All Grades (Occurring in ≥2 Patients) and Grades 3 to 5 (Occurring in ≥1 Patient)

Treatment-related Adverse Events (N = 26)	All Grades (n [%])	Grades 3-5	
		n (%)	Grade
Any	22 (85)	3 (12)	—
Fatigue	8 (31)	—	—
Diarrhea	4 (15)	—	—
Pruritus	4 (15)	—	—
Decreased appetite	4 (15)	—	—
Hypothyroidism	3 (12)	—	—
Nausea	3 (12)	—	—
Arthralgia	3 (12)	—	—
Myalgia	2 (8)	—	—
Anemia	2 (8)	1 (4)	3
Asthenia	2 (8)	—	—
ALT increase	2 (8)	—	—
AST increase	2 (8)	—	—
Blood bilirubin increase	2 (8)	—	—
Hepatitis	1 (4)	1 (4)	3
Interstitial lung disease	1 (4)	1 (4)	5
Dermatitis acneiform	1 (4)	1 (4)	3

ALT indicates alanine aminotransferase; AST, aspartate aminotransferase.

TABLE 3. Antitumor Activity of Pembrolizumab (10 mg/kg every 2 wk) in Patients With Advanced Salivary Gland Cancer Over a Median Follow-up of 20 Months (Range, 2 to 35 mo)

N = 26	n	
ORR (95% CI) (%)*	3	12 (2-30)
CR	0	0 (0-13)
PR	3†	12 (2-30)
SD	12	46 (27-67)
SD ≥ 6 mo	3	12 (2-30)
PD	11	42 (23-63)
Disease control rate (95% CI) (%)‡	15	58 (37-77)
Clinical benefit rate (95% CI) (%)§	6	23 (9-44)
Time to response, median (range) (mo)	3	1.9 (1.6-2.1)
Duration of response, median (range) (mo)	3	3.9 (3.5-20.6)

*ORR = CR+PR.
†Adenocarcinoma (n = 2); high-grade serous carcinoma (n = 1).
‡Disease control rate = CR+PR+SD.
§CR+PR+SD ≥6 months.
CI indicates confidence interval; CR, complete response; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease.

Statistical Analyses

A sequential monitoring approach was used to evaluate ORR within each cohort of KEYNOTE-028 after a minimum of 6 patients underwent ≥1 postbaseline scan. The type I error rate over multiple evaluations was controlled using the truncated sequential probability ratio test procedure at 0.08 (1-sided),[19] allowing simultaneous evaluation of efficacy and futility based on the number of patients with confirmed or unconfirmed response. Cohorts not closed for futility enrolled approximately 22 patients each. A sample of 22 evaluable patients would provide 80% power to demonstrate that the ORR exceeded 10% at an overall 1-sided 8% α level if the true best ORR for a cohort was 35%. PFS, OS, and duration of response were analyzed using the Kaplan-Meier method.

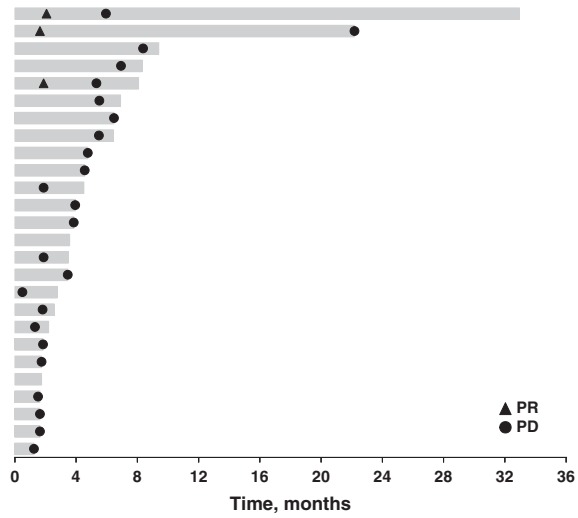

FIGURE 1. Treatment exposure to pembrolizumab and summary of best overall response assessed per RECIST by investigator review (N = 26). Patients with radiographic progression who were clinically stable or clinically improved, with no further evidence of RECIST progression on subsequent scans could continue treatment after consultation with the sponsor and at the investigator's discretion. PD indicates progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors version 1.1.

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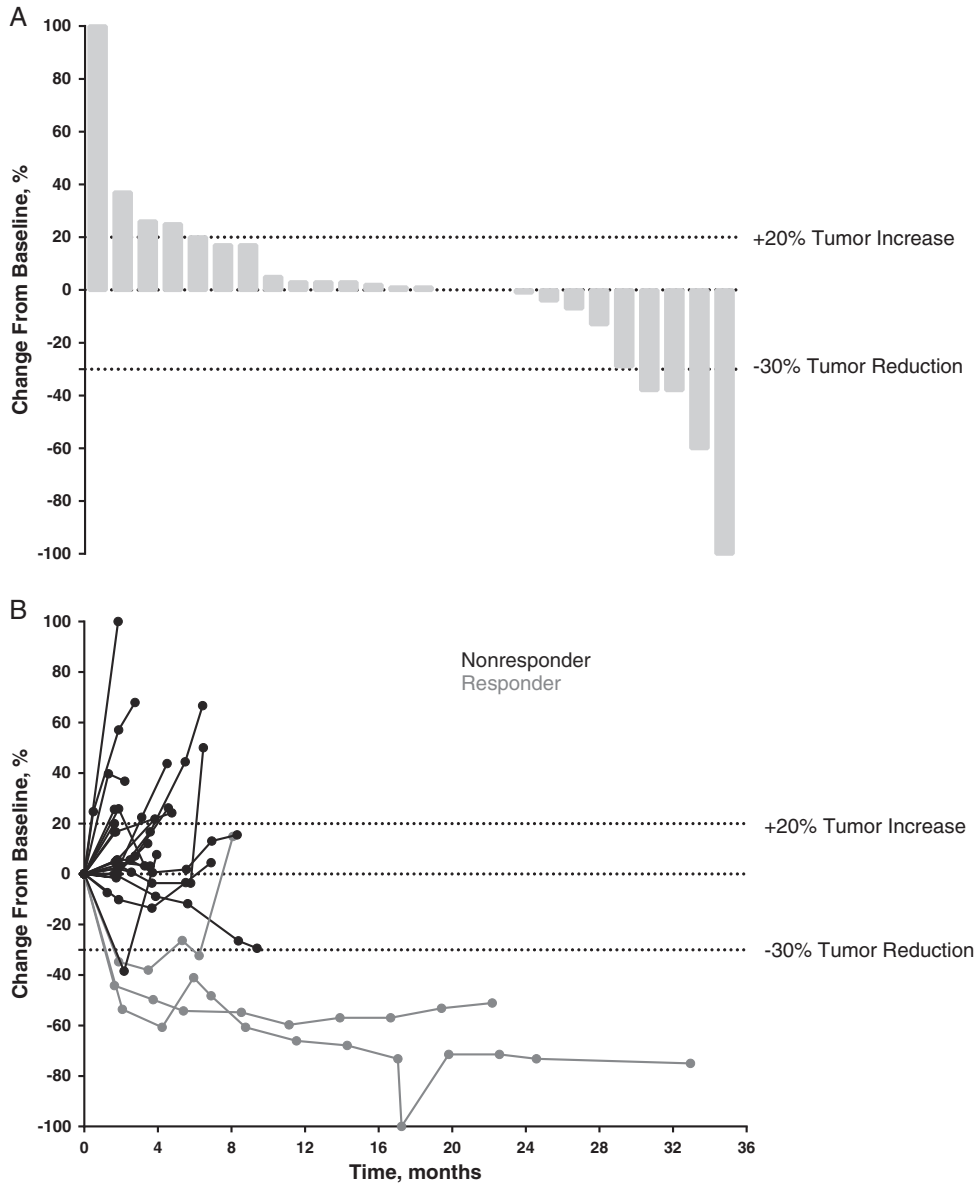

FIGURE 2. Waterfall plot of best percentage change from baseline (A) and percentage change from baseline in the sum of the longest diameters of target lesions (B) as assessed per Response Evaluation Criteria in Solid Tumors by investigator review (N = 26).

The efficacy population was composed of patients who received ≥1 dose of pembrolizumab and had measurable disease at baseline per RECIST. The safety population included all patients who received ≥1 dose of pembrolizumab. The data cutoff for this analysis was February 20, 2017.

RESULTS

Patient Characteristics

Overall, 142 patients with advanced SGC were screened, 102 patients did not pass the screening stage because they were PD-L1 negative, and 7 did not pass because they did not provide adequate tissue for biomarker analysis. Thirty-three (23%) patients had PD-L1-positive tumors, 26 of these patients were enrolled, and all received ≥1 dose of pembrolizumab (safety population). The median age was 57 years (range, 23 to 72 y). The majority were men (88%) and had ECOG PS 1 (73%) (Table 1). The most common subtype of SGC was adenocarcinoma (38%), followed by mucoepidermoid (12%), undifferentiated (8%), squamous cell (8%), and adenoid cystic (8%) carcinoma. Six patients (23%) received ≥3 prior lines of therapy for advanced disease. At the cutoff date, 24 patients had discontinued treatment, most commonly because of PD (n = 15) or AEs (n = 5); 2 patients remained on treatment. Among the 26 PD-L1-positive patients enrolled in this cohort, 12 (46%) were PD-L1 positive in the tumor only, 10 (38%) were positive in the stroma only, and 6 (23%) were positive in the tumor and the stroma.

Safety

Treatment-related AEs occurred in 22 patients (85%); the most frequently occurring were fatigue (n = 8), diarrhea (n = 4), pruritus (n = 4), and decreased appetite (n = 4) (Table 2). Grade

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≥3 treatment-related AEs were experienced by 3 patients (12%): anemia (grade 3) in 1, hepatitis (grade 3) in 1, and dermatitis acneiform (grade 3) and interstitial lung disease (grade 5) in 1. Six patients (23%) experienced immune-mediated AEs, including 4 cases of hypothyroidism (3 grade 2, one grade 1), 1 case of hepatitis (grade 3), and 1 case of interstitial lung disease (grade 5). There was 1 treatment-related death from interstitial lung disease in a 66-year-old man; however, a history of tuberculosis, malignant pleural effusions, and possible pulmonary infection were noted as possible confounding factors. Other treatment-related AEs that led to discontinuation were grade 2 arthritis and grade 3 hepatitis (n = 1 each).

Antitumor Activity

Three patients achieved PR (there were no CRs) for an ORR of 12% (Table 3). An additional 12 (46%) patients experienced stable disease (SD; defined as tumor shrinkage or growth insufficient to qualify as PR or PD, respectively) for a disease control rate (CR+PR+SD) of 58%. PRs were observed in patients with adenocarcinoma (n = 2) and high-grade serous carcinoma (n = 1). Two of these patients had PD-L1 expression in the stroma only (1 with adenocarcinoma and 1 with high-grade serous) and 1 patient with adenocarcinoma had PD-L1 expression in the tumor only. As of the data cutoff, no responses were ongoing (Fig. 1). A reduction in tumor size (sum of the longest tumor diameters) was documented for 35% (n = 9) of evaluable patients (N = 26) and was generally maintained over time (Fig. 2); 5 of these patients had adenocarcinoma, whereas the remaining 4 had high-grade serous, dedifferentiated acinic cell, adenoid cystic, and undifferentiated carcinoma. Over a median follow-up of 20 months (range, 2 to 35 mo), median time to response and duration of response were 2 and 4 months, respectively (Table 3). A best response of PD occurred in 11 patients (42%).

Median PFS was 4 months (95% confidence interval, 2 to 5); 6- and 12-month PFS rates were 17% and 4%, respectively (Fig. 3A). Median OS was 13 months (95% confidence interval, 6 mo to not reached); 6- and 12-month OS rates were 76% and 53%, respectively (Fig. 3B).

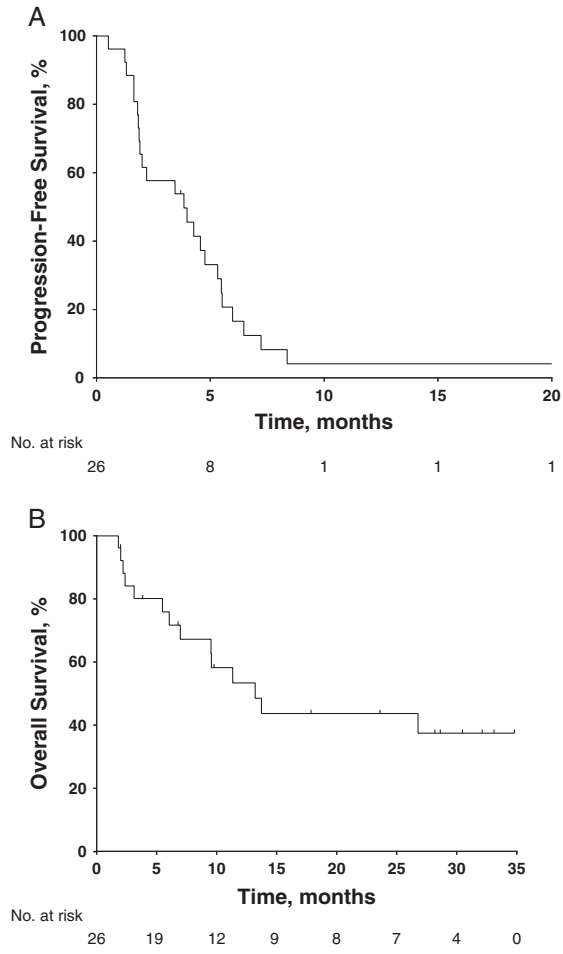

FIGURE 3. Kaplan-Meier estimates of (A) progression-free survival per Response Evaluation Criteria in Solid Tumors by investigator review and (B) overall survival (N = 26).

DISCUSSION

Pembrolizumab monotherapy was generally well tolerated in advanced SGC, with a safety profile that reflects previous experience of pembrolizumab in patients with advanced cancers. Promising antitumor activity was observed (disease control rate, 58%); durable responses were reported in patients with heavily pretreated, PD-L1-positive advanced SGC (median duration of response, 4 mo). Three patients experienced PR and 12 patients had SD; 3 patients had SD ≥6 months. PR occurred in 2 patients with adenocarcinoma and 1 with high-grade serous carcinoma; tumor shrinkage was observed primarily in patients with adenocarcinoma (n = 5), the most prevalent histologic type in this cohort (10 of 26 patients).

There is no gold standard for management of advanced SGC, and existing therapies generally lack significant clinical benefit. Available data supporting use of traditional cytotoxic chemotherapy are based on small studies, many of which were conducted before contemporary analytical concepts (eg, RECIST).[1] SGC tumor heterogeneity further complicates the assessment of treatments because different subtypes seem to respond differently to different chemotherapies.[20] Furthermore, objective responses with other targeted therapies are rarely reported.[4] Nonetheless, the ORR (12%) and OS (13 mo) with pembrolizumab lie within the reported ranges for response rates and OS seen with chemotherapies. In addition, the ORR is higher than the ORR reported with sorafenib (9%) and dovitinib (11%) in adenoid cystic carcinoma.[21,22] Median PFS (4 mo) and OS in the current study are lower than those reported with sorafenib (11 and 20 mo, respectively), and median PFS is lower than that reported for dovitinib (8 mo).[21,22] These disparate findings could be, in part, attributable to differences in follow-up time and treatment durations, as well as the mixed-subtype population studied here. Clinical trials with larger and more homogeneous populations with respect to SGC subtype are warranted to elucidate the relative effectiveness of treatment strategies for this disease.

In conclusion, pembrolizumab monotherapy has antitumor activity in patients with PD-L1-positive SGC. The safety profile of pembrolizumab was acceptable, although 1 death occurred owing to an occurrence of immune-related toxic effect interstitial lung disease. Because there is a lack of effective standard treatments for patients with SGC, the antitumor activity of pembrolizumab is a notable finding and justifies further investigation of immune checkpoint inhibitors in SGC. The clinical activity of a fixed dose of pembrolizumab in SGC (all histologies except sarcomas and mesenchymal tumors) is being investigated further in the multicohort, phase 2 KEYNOTE-158 trial (NCT02628067). Future trials in SGC

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must determine which patients and disease subtypes are likely to benefit from therapy with pembrolizumab.

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