European Journal of Cancer 171 (2022) 259–268

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Original Research

Evaluation of pembrolizumab monotherapy in patients with previously treated advanced salivary gland carcinoma in the phase 2 KEYNOTE-158 study

Caroline Even [a,*], Jean-Pierre Delord [b], Katharine A. Price [c], Kazuhiko Nakagawa [d], Do-Youn Oh [e,m], Matthew Burge [f], Hyun C. Chung [g], Toshihiko Doi [h], Marwan Fakih [i], Shunji Takahashi [j], Lili Yao [k], Fan Jin [k], Kevin Norwood [k], Aaron R. Hansen [l]

[a] *Gustave Roussy, Villejuif, France*
[b] *Institut Claudius Regaud, IUCT-Oncopole, Toulouse, France*
[c] *Mayo Clinic, Rochester, MN, USA*
[d] *Kindai University Hospital, Osaka, Japan*
[e] *Department of Internal Medicine, Seoul National University Hospital, Seoul, Republic of Korea*
[f] *Royal Brisbane and Women's Hospital and University of Queensland, Herston, QLD, Australia*
[g] *Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, Republic of Korea*
[h] *National Cancer Center Hospital East, Kashiwa, Japan*
[i] *City of Hope National Medical Center, Duarte, CA, USA*
[j] *Cancer Institute Hospital of the Japanese Foundation for Cancer Research, Tokyo, Japan*
[k] *Merck & Co., Inc., Rahway, NJ, USA*
[l] *Princess Margaret Cancer Centre, Toronto, ON, Canada*
[m] *Cancer Research Institute, Seoul National University College of Medicine, Integrated Major in Innovative Medical Science, Seoul National University Graduate School, Seoul, Republic of Korea*

Received 18 February 2022; received in revised form 10 May 2022; accepted 15 May 2022
Available online 28 June 2022

KEYWORDS
Salivary gland neoplasms;
Immune checkpoint inhibitors;
Clinical trial

Abstract ***Aim:*** We evaluated pembrolizumab monotherapy in patients with advanced salivary gland carcinoma on the phase 2 KEYNOTE-158 study (NCT02628067).
Methods: Eligible patients had histologically/cytologically confirmed advanced salivary gland carcinoma with prior failure or intolerance to standard therapy, measurable disease per Response Evaluation Criteria in Solid Tumours (RECIST) v1.1., and ECOG performance status 0–1. Patients were enrolled irrespective of tumour PD-L1 expression. Patients received pembrolizumab 200 mg Q3W for up to 35 cycles (~2 years). Radiographic imaging occurred every 9 weeks through month 12, then every 12 weeks. PD-L1 positivity was defined as

* *Corresponding author*: Gustave Roussy 114 rue Edouard Vaillant 94805 Villejuif, France.
E-mail address: Caroline.EVEN@gustaveroussy.fr (C. Even).

https://doi.org/10.1016/j.ejca.2022.05.007

combined positive score ≥1 (evaluated using PD-L1 IHC 22C3 pharmDx). The primary endpoint was objective response rate per RECIST v1.1.

Results: In total, 109 patients were enrolled (PD-L1–positive, 25.7%). At the data cutoff (October 5, 2020), median follow-up was 53.3 (range, 50.8–56.3) months. Objective response rate was 4.6% (95% CI, 1.5–10.4%) among all patients (complete response, n = 1; partial response, n = 4) and was 10.7% (95% CI, 2.3–28.2%) in patients with PD-L1–positive disease and 2.6% (95% CI, 0.3–9.1%) in patients with PD-L1–negative disease. Duration of response was ≥24 months for all 5 responders; median duration of response was not reached (range, 25.1–49.8+ months). Median progression-free survival and overall survival were 4.0 (95% CI, 2.6–4.2) and 21.1 (95% CI, 15.9–25.5) months, respectively. Treatment-related adverse events occurred in 75.2% (grade 3–4, 15.6%; grade 5, 0%) of patients. Immune-mediated adverse events occurred in 22.0% of patients (grade 3, 5.5%; grade 4–5, 0).

Conclusions: A small subset of patients with advanced salivary gland carcinoma treated with pembrolizumab had a response; all had response duration ≥2 years. The safety profile of pembrolizumab was manageable.

1. Introduction

Salivary gland cancers are rare cancers with incidence rates that vary by region [1]. Globally, malignant salivary gland cancers are estimated to occur in 0.4–2.6/100,000 individuals each year [1,2]. Outcomes are particularly poor for patients who develop metastatic disease [3–5]. Although 5-year survival estimates for patients with localised disease are 95%, estimates for patients with distant metastases are 15%–44% [4,6,7], with lower estimates for patients with high-grade, unresectable tumours [4,8].

Treatment options are limited for patients with recurrent, unresectable, or metastatic salivary gland tumours. No systemic treatments have an indication for salivary gland cancer, and cisplatin-based regimens are the only systemic approach that is generally recommended by the National Comprehensive Cancer Network [9]. These regimens confer moderate activity, with overall response rates of 27%–44%, but the median duration of response (DOR) is limited (7–15+ months) [10,11]. Current National Comprehensive Cancer Network and ASCO clinical practice guidelines provide support for certain targeted therapies (anti–vascular endothelial growth factor receptor inhibitors; neurotrophic tyrosine receptor kinase [NTRK] therapy for *NTRK* gene fusion-positive tumours; anti–human epidermal growth factor receptor 2 [HER2] therapy for HER2-positive tumours; anti-androgen therapy for androgen receptor–positive tumours) and immunotherapies (for tumours with high tumour mutation burden [TMB-high]) [9,12]. However, given the poor outcomes for patients with advanced salivary gland cancer, a need exists for treatments that elicit more durable responses in a broad range of patients.

The anti–programmed death 1 (PD-1) monoclonal antibody pembrolizumab has demonstrated antitumour activity in multiple tumour types, including in patients with salivary gland cancer [13]. The phase 1b KEYNOTE-028 study (ClinicalTrials.gov, NCT02054806) enrolled a cohort of 26 patients with programmed death ligand 1 (PD-L1)-positive advanced salivary gland cancer [13]. The objective response rate (ORR) in this cohort was 12% (95% CI, 2–30%) and included three partial responses (PRs), with a median DOR of 3.9 months (range, 3.5–20.6 months). Treatment-related adverse events (AEs) were reported for 85% of patients.

KEYNOTE-158 (ClinicalTrials.gov, NCT02628067) is an open-label, phase 2, multicohort study evaluating pembrolizumab monotherapy in patients with one of 10 rare cancer types, and in patients with advanced solid tumours assessed as high microsatellite instability (MSI-H) or TMB-high. Herein, we report results from the cohort of patients with previously treated salivary gland cancer in KEYNOTE-158. In contrast to the phase 1b KEYNOTE-028 study, patients were enrolled in KEYNOTE-158 irrespective of tumour PD-L1 expression. Evaluation of outcomes by tumour biomarker status was a prespecified study objective.

2. Methods

2.1. Study design and ethics

The ongoing KEYNOTE-158 study is a phase 2, single-arm, multicentre, multicohort, open-label study evaluating pembrolizumab monotherapy. Cohort J, for which enrolment is complete, includes patients with salivary gland carcinoma.

Patients ≥18 years old were eligible to enrol in cohort J if they had histologic or cytologic confirmation of advanced, unresectable, and/or metastatic salivary gland carcinoma, excluding sarcomas and mesenchymal tumours, that was deemed incurable and for which prior standard first-line therapy had failed. Tumours must have progressed on or been intolerant to therapies known to provide clinical benefit. Eligible patients had measurable disease per Response Evaluation Criteria in Solid Tumours (RECIST), version 1.1, confirmed by independent central radiologic review, Eastern Cooperative Oncology Group performance status of 0 or 1, life expectancy of at least 3 months, and adequate haematologic and organ function. Patients were required to provide a tumour sample at screening for assessment of PD-L1 status but were enrolled irrespective of biomarker status.

Patients were excluded from the study if they had any of the following: a diagnosis of immunodeficiency or receipt of systemic steroid therapy or other immunosuppressive therapy within 7 days before receiving pembrolizumab; active autoimmune disease that required systemic treatment within the previous 2 years; prior anticancer monoclonal antibody treatment within 4 weeks before study day 1; received chemotherapy, targeted small-molecule therapy, or radiation therapy within 2 weeks before study day 1; other known malignancy within 2 years before enrolment (exceptions were curatively treated basal or squamous cell carcinoma and curatively resected in situ cancers); active central nervous system metastasis and/or carcinomatous meningitis; glioblastoma multiforme; or history or current evidence of noninfectious pneumonitis requiring steroids.

The study was conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonisation Good Clinical Practice guidelines, and all applicable local and/or national regulations. At each study site, the appropriate institutional review board(s) or independent ethics committee(s) approved the protocol and informed consent forms before the first patient was enrolled. All patients provided written informed consent to participate.

2.2. Study treatment

Pembrolizumab 200 mg was administered as an intravenous infusion once every 3 weeks for up to 35 cycles (approximately 2 years) or until disease progression, unacceptable toxicity, intercurrent illness that prevented further pembrolizumab treatment, noncompliance with the protocol, patient pregnancy, or physician or patient decision. Clinically stable patients with radiologic progression could remain on treatment until progression was confirmed on subsequent imaging assessment. Patients who attained complete response (CR) were permitted to stop pembrolizumab treatment after receiving at least eight treatment cycles. Eligible patients who completed a full course (35 cycles) of pembrolizumab and achieved stable disease (SD), PR, or CR, or who discontinued treatment early after attaining CR, were allowed to receive up to 1 year of additional pembrolizumab therapy if they had subsequent radiologic disease progression.

2.3. Assessments

PD-L1 status was assessed centrally using the PD-L1 IHC 22C3 pharmDx assay (Agilent Technologies, Carpinteria, CA, USA). PD-L1 status was defined according to the combined positive score (CPS), which was calculated as the number of PD-L1–staining cells (tumour cells, lymphocytes, and macrophages) divided by the total number of viable tumour cells, multiplied by 100. PD-L1–positive tumours were defined as CPS ≥1; PD-L1–negative tumours were defined as CPS <1. Tumour TMB status was assessed using the FoundationOne CDx assay. TMB-high tumours were defined as having at least 10 mutations per megabase. MSI status was assessed retrospectively at a central laboratory (Almac Group, Craigavon, UK), using PCR-based assays to analyse five tumour microsatellite loci (BAT25, BAT26, NR21, NR24, and Mono27), as described previously [14].

Tumour imaging (using computed tomography [preferred] or magnetic resonance imaging) was conducted at baseline, every 9 weeks for 12 months, and every 12 weeks thereafter. Imaging was continued until disease progression, the start of new anticancer treatment, withdrawal of consent, or death.

Safety assessments included the evaluation of new or worsening AEs at all study visits, including the 30-day safety follow-up (90-day follow-up 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 (CTCAE) version 4.0.

2.4. Study endpoints

The primary efficacy endpoint was the ORR, defined as the proportion of patients with CR or PR according to RECIST version 1.1, as determined by independent central radiologic review. ORR was analysed for the cohort overall and in subgroups defined according to tumour PD-L1 status. Secondary efficacy endpoints included DOR, defined as the time from first documented evidence of CR or PR until disease progression or death; progression-free survival (PFS), defined as the time from first dose of study treatment to the first documented disease progression according to RECIST version 1.1, by independent central review, or death; and overall survival (OS), defined as the time from first dose of study treatment to death. The primary safety endpoint was the incidence of AEs.

2.5. Statistical analyses

The study was planned to enrol approximately 100 patients in cohort J regardless of the biomarker status of the primary tumour. No statistical hypothesis testing was planned for the study. Efficacy and safety analyses included all patients who received ≥1 dose of pembrolizumab. Analyses of ORR used point estimates, accompanied by Clopper–Pearson 95% CIs. DOR, PFS, and OS were analysed using the Kaplan–Meier method. Statistical analyses were done using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

3. Results

3.1. Patients

Between January 28, 2016, and July 12, 2016, 109 patients were enrolled at 36 sites in 13 countries. All patients received at least one dose of pembrolizumab and were included in the efficacy analyses. As of the data cutoff (October 5, 2020), nine patients (8.3%) had completed pembrolizumab treatment and 100 (91.7%) had discontinued treatment, including 85 (78.0%) who discontinued because of clinical or radiographic disease progression, 10 (9.2%) who withdrew consent, and 5 (4.6%) who discontinued because of an AE. Three patients (2.8%) received a second course of pembrolizumab, all of whom received all 17 doses during the second course of treatment. The median time from first dose to data cutoff was 53.3 (range, 50.8–56.3) months. Patients had a median (range) age of 60.0 (22–82) years (Table 1). All patients had stage IV disease, and 28 patients (25.7%) had PD-L1–positive tumours (i.e., PD-L1 CPS ≥1). Twenty-two patients (20.2%) had received more than two prior lines of systemic therapy, and a majority received prior radiation therapy (n = 94 [86.2%]).

Table 1
Patient demographics and baseline characteristics.

Characteristic	All patients N = 109
Age, median (range), y	60.0 (22–82)
<65 y	77 (70.6)
Sex	
Men	54 (49.5)
Women	55 (50.5)
ECOG performance status	
0	58 (53.2)
1	51 (46.8)
Metastatic stage	
M0	2 (1.8)
M1	107 (98.2)
Disease stage	
IV	22 (20.2)
IVB	1 (0.9)
IVC	86 (78.9)
Histologic subtype[a]	
Adenoid cystic carcinoma	59 (54.1)
Adenocarcinoma	25 (22.9)
Other	25 (22.9)
Number of prior lines of systemic therapy	
0	15 (13.8)
1	46 (42.2)
2	26 (23.9)
3 or more	22 (20.2)
Received prior radiation therapy	94 (86.2)
PD-L1 status	
CPS <1	77 (70.6)
CPS ≥1	28 (25.7)
Not evaluable[b]	4 (3.7)
TMB status	
TMB-high (≥10 mut/Mb)	3 (2.8)
Non–TMB-high (<10 mut/Mb)	79 (72.5)
Unknown[b]	27 (24.8)
MSI status	
MSI-high[c]	1 (0.9)
Non–MSI-high	100 (91.7)
Missing[b]	8 (7.3)

CPS, combined positive score; ECOG, Eastern Cooperative Oncology Group; MSI, microsatellite instability; PD-L1, programmed death ligand 1; TMB, tumour mutational burden.
Values are presented as n (%) unless stated otherwise.
[a] A complete description of patients' tumour histology is provided in Supplemental Table 1.
[b] Tissue sample not available or inadequate for evaluation of biomarker expression.
[c] MSI-high status was determined using PCR-based central testing evaluating five mononucleotide loci, as described previously [14].

3.2. Antitumour activity

The ORR in the total population was 4.6% (95% CI, 1.5–10.4%), with one CR and four PRs (Table 2). For the five patients who achieved a PR (n = 4) or CR (n = 1), the median time to response was 2.0 months (range, 1.9–4.2 months). The DOR exceeded 24 months for all patients who had a response; the median DOR was not reached (range, 25.1 to 49.8+ months) (Fig. 1). At the data cutoff, four of the five responders had not progressed (one had an ongoing response and three had been censored because their last adequate assessment was ≥5 months prior to the data cutoff date).

Of the 103 patients who had at least one postbaseline tumour assessment, a reduction in the size of target lesions relative to baseline was observed for 24 patients (23.3%), including eight (7.8%) who had at least a 30% reduction in tumour size (Fig. 2). Among these eight patients, reductions were observed in patients with a variety of baseline characteristics, including tumour histology (adenocarcinoma, n = 3; adenoid cystic carcinoma, n = 2; squamous cell carcinoma, n = 1; epithelial-myoepithelial carcinoma of the left parotid, n = 1; mucinous carcinoma, n = 1) and prior therapy (1 line, n = 5; ≥2 lines, n = 3).The disease control rate, defined as the proportion of patients who achieved CR, PR, or SD, was 53.2% (n = 58).

The ORR was 10.7% (95% CI, 2.3–28.2%) among the 28 patients with PD-L1–positive tumours (CPS ≥1) and included three patients who attained PR. The ORR

Table 2
Antitumour activity of pembrolizumab, according to RECIST version 1.1 criteria, as assessed by blinded independent central radiologic review.[a]

Assessment	All patients (N = 109)	Patients with PD-L1–positive tumours[a] (n = 28)	Patients with PD-L1–negative tumours[a] (n = 77)
ORR, n (95% CI)[b]	4.6 (1.5–10.4)	10.7 (2.3–28.2)	2.6 (0.3–9.1)
Best overall response, n (%)			
CR	1 (0.9)	0	1 (1.3)
PR	4 (3.7)	3 (10.7)	1 (1.3)
SD[c]	53 (48.6)	9 (32.1)	43 (55.8)
Non-CR/non-PD	1 (0.9)	0	1 (1.3)
PD	42 (38.5)	11 (39.3)	29 (37.7)
Not evaluable[d]	5 (4.6)	4 (14.3)	0
No assessment[e]	3 (2.8)	1 (3.6)	2 (2.6)
Time to response, median (range), months	2.0 (1.9–4.2)	–	–
DOR, median (range), months	Not reached (25.1–49.8+)	–	–
Patients with response ≥24 months, n (%)	5 (100.0)	–	–

CR, complete response; DOR, duration of response; ORR, objective response rate; PD, progressive disease; PD-L1, programmed death ligand 1; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.
[a] Four patients (3.7%) had tumours that were not evaluable for tumour PD-L1 status. PD-L1 status was not assessed in three patients (2.8%). PD-L1 status was determined according to a combined positive score ≥1 for PD-L1–positive or <1 for PD-L1–negative.
[b] Includes patients with confirmed CR or PR. At the time of analysis, all responses were confirmed.
[c] Best overall response assessment required SD of at least 6 weeks in duration.
[d] Two patients had imaging results showing SD within 42 days of randomisation but had no subsequent imaging and were therefore classified as not evaluable. Three patients had missing anatomies or non-evaluable lesions.
[e] No postbaseline assessment available for response evaluation.

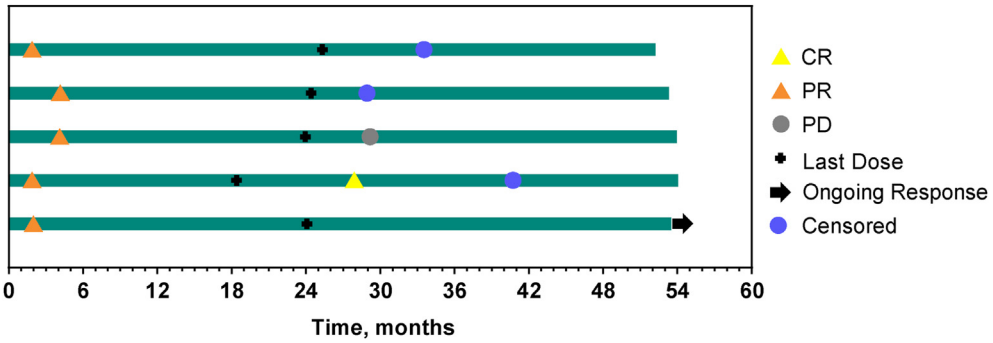

Fig. 1. Time to response and duration of response. Response (i.e., patients with complete or partial response) was assessed according to Response Evaluation Criteria in Solid Tumors version 1.1 criteria by independent central review. Green bar indicates duration of follow-up. CR, complete response; PD, progressive disease; PR, partial response.

was 2.6% (95% CI, 0.3–9.1%) among the 77 patients with PD-L1–negative tumours (CPS <1) and included one patient with a CR and one with a PR. Confirmed objective response was achieved in one patient (33.3%) with TMB-high disease and three (3.8%) with non-TMB-high disease. One further patient with a response had unknown TMB status. Additionally, confirmed objective response was achieved in one patient (100%) with MSI-high disease and four (4.0%) with non-MSI-high disease. One patient in the cohort had a tumour that was both MSI-H and TMB-high and achieved a CR.

3.3. Progression-free survival and overall survival

At data cutoff, 101 patients (92.7%) had experienced disease progression or death. Median PFS was 4.0 (95% CI, 2.6–4.2) months; the estimated 6-, 12-, and 24-month PFS rates were 35.8%, 14.2%, and 10.9%, respectively (Fig. 3A).

Eighty-three patients (76.1%) died during the study. Median OS was 21.1 (95% CI, 15.9–25.5) months; the estimated 24-, 36-, and 48-month OS rates were 44.9%, 32.7%, and 23.2%, respectively (Fig. 3B).

3.4. Safety

Treatment-related AEs occurred in 82 of 109 (75.2%) patients (Table 3). The most frequently occurring treatment-related AEs were fatigue (n = 29 [26.6%]), asthenia (n = 16 [14.7%]), pruritus (n = 15 [13.8%]), diarrhoea (n = 13 [11.9%]), and hypothyroidism (n = 12 [11.0%]). Sixteen patients (14.7%) experienced grade 3 events and one (0.9%) experienced a grade 4

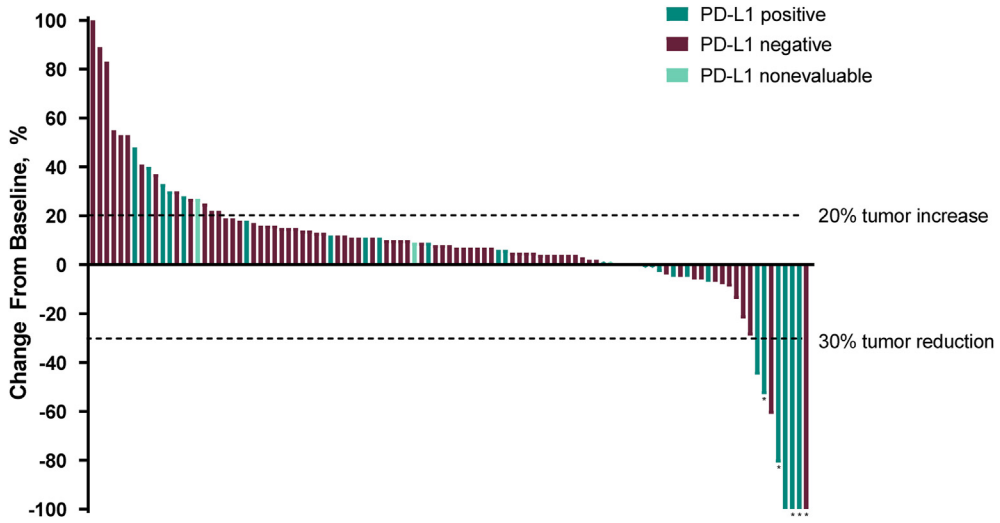

Fig. 2. Best percentage change from baseline in target lesion size. Change from baseline in target lesion size was assessed according to Response Evaluation Criteria in Solid Tumors version 1.1 criteria by independent central radiologic review (N = 99). Percentage changes >100% are presented as 100%. PD-L1, programmed death ligand 1. a Eight patients had a >30% reduction in tumour size; three patients also developed new lesions and were therefore not assessed as having an objective response. Tumour histology in these patients was adenocarcinoma (n = 3), adenoid cystic carcinoma (n = 2), squamous cell carcinoma (n = 1), epithelial-myoepithelial carcinoma of the left parotid (n = 1), and mucinous carcinoma (n = 1). Asterisks indicate patients with a confirmed objective response.

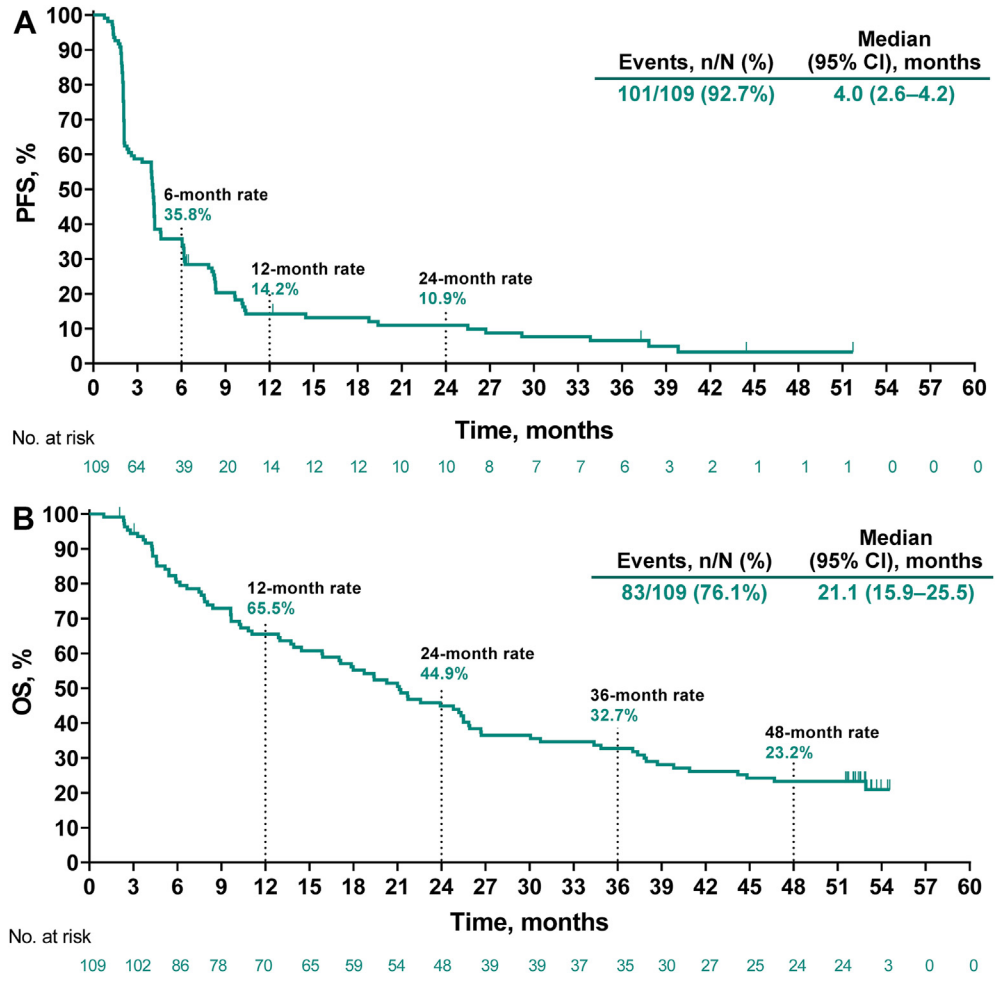

Fig. 3. (A) Progression-free survival and (B) overall survival. PFS was assessed according to Response Evaluation Criteria in Solid Tumors version 1.1 criteria by independent central review. PFS, progression-free survival.

Table 3
Adverse events.

Adverse events, n (%)	All patients N = 109	
Any treatment-related AE	82 (75.2)	
Grade 3–4	17 (15.6)[a]	
Grade 5	0	
Led to treatment discontinuation	5 (4.6)	
Treatment-related AEs occurring in ≥5% of patients	Any Grade	Grade 3–4
Fatigue	29 (26.6)	3 (2.8)
Asthenia	16 (14.7)	0
Pruritus	15 (13.8)	0
Diarrhoea	13 (11.9)	0
Hypothyroidism	12 (11.0)	0
Arthralgia	10 (9.2)	1 (0.9)
Rash	10 (9.2)	1 (0.9)
Decreased appetite	9 (8.3)	0
Stomatitis	7 (6.4)	0
Nausea	6 (5.5)	0
Maculopapular rash	6 (5.5)	0
Weight decreased	6 (5.5)	0
Immune-mediated AEs	Any Grade	Grade 3[b]
Any immune-mediated AE[c,d]	24 (22.0)	6 (5.5)
Hypothyroidism	13 (11.9)	0
Hyperthyroidism	6 (5.5)	0
Adrenal insufficiency	3 (2.8)	1 (0.9)
Colitis	2 (1.8)	2 (1.8)
Pneumonitis	2 (1.8)	0
Severe skin reactions	2 (1.8)	1 (0.9)
Hepatitis	1 (0.9)	0
Hypophysitis	1 (0.9)	0
Pancreatitis	1 (0.9)	1 (0.9)
Type 1 diabetes mellitus	1 (0.9)	1 (0.9)

AE, adverse event.
[a] Only one grade 4 event occurred (diplopia).
[b] No grade 4 or 5 immune-mediated AEs occurred.
[c] Immune-mediated AEs were reported based on a list of terms specified at the time of analysis and included regardless of attribution to study treatment or immune relatedness by the investigator. Related terms were included.
[d] There were no infusion reactions.

event (diplopia). No grade 5 treatment-related AEs occurred. Fatigue (n = 3 [2.8%]), colitis (n = 2 [1.8%]), and hypophosphatemia (n = 2 [1.8%]) were the only treatment-related grade 3 or 4 events that occurred in more than one patient. Five patients (4.6%) discontinued pembrolizumab because of a treatment-related AE.

Immune-mediated AEs (reported based on a list of terms specified at the time of analysis and included regardless of attribution to study treatment) occurred in 24 patients (22.0%) (Table 3). The most frequent of these were hypothyroidism (n = 13 [11.9%]), hyperthyroidism (n = 6 [5.5%]), and adrenal insufficiency (n = 3 [2.8%]). Grade 3 immune-mediated AEs were reported for six patients (5.5%), and no grade 4 to 5 immune-mediated AEs occurred. Four patients (3.7%) discontinued treatment owing to an immune-mediated AE. No infusion reactions were reported.

4. Discussion

In this analysis from the KEYNOTE-158 study, pembrolizumab demonstrated antitumour activity with durable response in a subset of patients with previously treated advanced salivary gland carcinoma. In the overall cohort, 4.6% of patients had an objective response. All responses were maintained for at least 2 years, and at a median follow-up of more than 4 years, the median DOR was not reached. Although responses occurred in only a subset of patients, the durability of the responses in this study was notable, particularly given the heavily pretreated patient population enrolled in this study (failure on or intolerance to standard therapy was an entry requirement). The median PFS was 4.0 months, and most patients experienced a PFS event within 6 months of study entry. The median OS was 21.1 months and approximately one third of patients remained alive at 3 years.

Our current findings build on earlier results from the phase 1b multicohort KEYNOTE-028 study of pembrolizumab monotherapy in 26 patients with PD-L1–positive advanced salivary gland carcinoma [13]. The ORR of 12% (n = 3) in KEYNOTE-028 is similar to the 10.7% (n = 3) ORR observed for patients with PD-L1–positive tumours in the current analysis of KEYNOTE-158. Our analysis expands on those previous findings by including patients with PD-L1–negative tumours, two of whom also attained response (2.6%), including one with a CR. In contrast to KEYNOTE-028, in which responders had a median DOR of 3.9 months (range, 3.5–20.6 months), the DOR in the current analysis was not reached (range, 25.1 to 49.8+ months). The OS was also longer in the current study than in KEYNOTE-028 (21.1 vs. 13 months). Given the limited number of responders in the overall cohort, it is difficult to evaluate whether tumour PD-L1 expression was associated with outcome in this population of patients with salivary gland cancer.

Very few patients in this study had MSI-H (n = 1) or TMB-high (n = 3) disease. One patient with MSI-H and TMB-high disease experienced a response, consistent with earlier reports from the KEYNOTE-158 study [14,15]. Taken together, these findings suggest that responses may be observed regardless of tumour biomarker status. However, the results are difficult to interpret given the small number of patients with MSI-H and TMB-high salivary cancer. Investigation of associations between other potential biomarkers and tumour response among patients with salivary gland cancer receiving pembrolizumab therapy could help address the unmet need in this setting.

Results from KEYNOTE-158 represent, to our knowledge, the largest data set describing outcomes among patients with salivary cancer receiving checkpoint inhibitor therapy. We have identified three other

clinical trials of immune checkpoint inhibitor therapy for patients with salivary gland tumours. A phase 2 study of nivolumab in 98 patients with recurrent or metastatic salivary gland cancer reported responses in 4 of 46 patients (8.7%) with adenoid cystic carcinoma (ACC) and 2 of 52 patients (3.8%) with non-ACC tumours (all responses were PRs) [16]. Another phase 2 study evaluated nivolumab plus ipilimumab for 64 patients with recurrent or metastatic salivary gland cancer. Among patients with ACC, 2 of 32 (6%) had an objective response [17], and among patients with non-ACC, 5 of 32 (16%) had an objective response (all responses were PRs) [18]. A phase 1 study of the PD-1 inhibitor JTX-4014 enrolled 2 patients with PD-L1–positive tumours. Both patients were reported to have durable responses to treatment although the details of those responses were not described [19]. Trials evaluating whether combining pembrolizumab with other agents can improve outcomes among patients with salivary gland cancer are ongoing. These trials are evaluating combinations of pembrolizumab with lenvatinib (NCT04209660), androgen-deprivation therapy (NCT03942653), the MDM-2 inhibitor APG-115 (NCT03781986), and chemotherapy (NCT03360890; NCT04895735).

The safety profile of pembrolizumab in patients with advanced salivary gland carcinoma was consistent with what was previously reported for pembrolizumab monotherapy in patients with advanced solid tumours; no unexpected safety signals were detected [13–15,20–22]. The nature and severity of treatment-related AEs experienced during the study was consistent with those reported in previous studies [13–15,20–22]. Few patients experienced AEs of grade 3/4 severity, and there were no treatment-related deaths.

Given the rarity of salivary gland cancer and paucity of studies in this tumour type, the findings from KEYNOTE-158 constitute a large and important data set for a treatment approach (immunotherapy) that has been only minimally explored in this setting. However, interpretation of the current results is limited by the single-arm study design, which was necessitated by the lack of an appropriate comparator therapy for this rare tumour type.

Pembrolizumab monotherapy demonstrated antitumour activity and durable responses in a small subset of patients with advanced salivary gland carcinoma. Responses were observed in patients with both PD-L1–positive and PD-L1–negative disease and irrespective of TMB or MSI status. These data represent the largest prospective evaluation of immunotherapy in patients with salivary gland cancer.

Author contributions

C Even had full access to all the data in the study and takes responsibility for the integrity and the accuracy of the data analysis, Conception, design, or planning of the study: JP Delord, T Doi, K Norwood, Acquisition, analysis, or interpretation of the data: All authors, Provision of study materials/patients: C Even, M Burge, HC Chung, M Fakih, Drafting of the manuscript: T Doi and K Norwood, Review of the manuscript for important intellectual content: All authors, Decision to submit the manuscript for publication: All authors.

Funding/support

Funding for this research was provided by Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

Role of the funding source

The sponsor was involved in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, and approval of the manuscript; and decision to submit the manuscript for publication.

Data sharing statement

Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA (MSD) is committed to providing qualified scientific researchers access to anonymised 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 US and EU 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.

Conflict of interest statement

C Even: research support from Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Rahway, NJ, USA (MSD); participant on advisory boards for Bristol Myers Squibb, MSD, Merck Serono, and Innate Pharma.

J-P Delord: funding to the institution for consulting or advisory roles with Novartis, Roche/Genentech, Bristol-Myers Squibb, MSD Oncology, and Pierre Fabre; research funding to the institution from Genentech, Bristol-Myers Squibb, MSD Oncology, AstraZeneca, and Transgene.

KA Price: no conflicts to report.

K Nakagawa: honoraria from Ono Pharmaceutical Co., Ltd., Merck Biopharma Co., Ltd., Amgen Inc., Taiyo Pharma Co., Ltd., Nippon Kayaku Co., Ltd., Takeda Pharmaceutical Co., Ltd., AstraZeneca K.K., Life Technologies Japan Ltd., Chugai Pharmaceutical Co., Ltd., Neo Communication, Eli Lilly Japan K.K., Novartis Pharma K.K., MSD K.K., Medical Mobile Communications Co., Ltd, Pfizer Japan Inc., Yodosha Co., Ltd., Nippon Boehringer Ingelheim Co., Ltd., CMIC ShiftZero K.K., Taiho Pharmaceutical Co.,Ltd., Japan Clinical Research Operations, Bayer Yakuhin, Ltd., CMIC Co., Ltd.; research funding from IQVIA Services Japan K.K., Eisai Co., Ltd., Syneos Health Clinical K.K., AstraZeneca K.K., EPS Corporation, Mochida Pharmaceutical Co., Ltd., Nippon Kayaku Co.,Ltd., Covance Japan Inc., EPS International Co.,Ltd., Japan Clinical Research Operations, Daiichi Sankyo Co., Ltd., Otsuka Pharmaceutical Co., Ltd., Takeda Pharmaceutical Co.,Ltd., GlaxoSmithKline K.K., MSD K.K., Sanofi K.K., Ono Pharmaceutical Co.,Ltd., Chugai Pharmaceutical Co.,Ltd., Amgen Inc., Nippon Boehringer Ingelheim Co., Ltd., Taiho Pharmaceutical Co.,Ltd., SRL, Inc., EP-CRSU Co., Ltd. Medical Research Support, Mebix, Inc., Eli Lilly Japan K.K., Bristol-Myers Squibb K.K., Novartis Pharma K.K., Janssen Pharmaceutical K.K.; Consulting/advisory role with Eli Lilly Japan K.K., Ono Pharmaceutical Co.,Ltd.; patents from Daiichi Sankyo Co., Ltd.

D-Y Oh: consultant/advisory board for AstraZeneca, Novartis, Genentech/Roche, Merck Serono, Bayer, Taiho, ASLAN, Halozyme, Zymeworks, BMS/Celgene, BeiGene, Basilea, Turning Point, and Yuhan; research grants from AstraZeneca, Novartis, Array, Eli Lilly, Servier, BeiGene, MSD, and Handok.

M Burge: honoraria from Merck.

HC Chung: funding to the institution from Merck Sharp & Dohme, Lilly, GSK, Merck-Serono, BMS/Ono, Taiho, Amgen, Beigene, Incyte, Zymeworks; advisory boards for Taiho, Celltrion, Merck Sharp & Dohme, Lilly, BMS, Merck-Serono, Gloria, Beigene, Amgen, Zymework; honoraria for lectures from Merck-Serono, Eli Lilly.

T Doi: grants from Pfizer, Lilly, Quintiles (IQVIA), Eisai, Merck Serono, Bristol-Myers Squibb, AbbVie, MSD, Daiichi Sankyo, Sumitomo Dainippon, Taiho, Novartis, Janssen, and Boehringer Ingelheim; personal fees from Chugai Pharma, Amgen, Takeda, Bayer, Rakuten Medical, Ono Pharmaceutical, Astellas Pharma, Oncolys BioPharma, Otsuka Pharma, Bristol-Myers Squibb, AbbVie, MSD, Daiichi Sankyo, Sumitomo Dainippon, Taiho, Novartis, Janssen, and Boehringer Ingelheim.

M Fakih: consultant to Zhuhai Yufan Biotechnology Co., Ltd., Taiho Oncology, Pfizer Inc, HalioDx, Bayer Corporation, and Mirati Therapeutics, Inc.; advisor to Amgen, Inc., Array BioPharma, Bayer Corporation GlaxoSmithKline, Mirati Therapeutics, Inc., and Seattle Genetics, Inc.; served on speakers' bureaus for Amgen, Inc. and Guardant360; grants to institution from Amgen, Inc., AstraZeneca Pharmaceuticals, Novartis Oncology, Bristol Myers Squibb, and Verastem.

S Takahashi: grants from MSD for the current study; grants and personal fees from Eisai, Novartis, Taiho Pharmaceutical Co., Chugai, Bayer, and Daiichi-Sankyo; grants from AstraZeneca.

L Yao: employee of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

F Jin: employee of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Rahway, NJ, USA. Owns stock in Merck & Co., Inc.

K Norwood: employee of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Rahway, NJ, USA. Owns stock in Merck & Co., Inc.

A Hansen: research funding to the institution from GSK, Merck, Pfizer, MedImmune/Genentech, Roche, Janssen, BMS, AstraZeneca, Astellas, Boehringer Ingelheim, and Bayer; consulting role/advisory boards for GSK, Merck, and Eisai.

Acknowledgements

The authors thank the patients and their families and caregivers for participating in this study, along with all investigators and site personnel. Alissa Moore and Jennifer Smedberg served as clinical scientists on the trial. Medical writing assistance was provided by Autumn Kelly, MA, of ICON plc (Blue Bell, PA, USA). This assistance was funded by Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2022.05.007.

References

[1] Eveson JW, Auclair P, Gnepp DR, El-Haggar AK. Tumours of the salivary glands: Introduction. In: Barnes L, Eveson JW, Reichart P, Sidransky D, editors. World Health Organization classification of tumours. Pathology & genetics: Head and neck tumours. WHO Press; 2005.

[2] Morales J, Li L, Fattah FJ, et al. Review of poly (ADP-ribose) polymerase (PARP) mechanisms of action and rationale for targeting in cancer and other diseases. Crit Rev Eukaryot Gene Expr 2014;24:15–28. https://doi.org/10.1615/critreveukaryotgeneexpr.2013006875.

[3] Nam SJ, Roh JL, Cho KJ, Choi SH, Nam SY, Kim SY. Risk factors and survival associated with distant metastasis in patients with carcinoma of the salivary gland. Ann Surg Oncol 2016;23:4376–83. https://doi.org/10.1245/s10434-016-5356-3.

[4] Mimica X, McGill M, Hay A, et al. Distant metastasis of salivary gland cancer: incidence, management, and outcomes. Cancer 2020;126:2153–62. https://doi.org/10.1002/cncr.32792.

[5] Ouyang DQ, Liang LZ, Zheng GS, et al. Risk factors and prognosis for salivary gland adenoid cystic carcinoma in southern China: a 25-year retrospective study. Medicine (Baltim) 2017;96:e5964. https://doi.org/10.1097/MD.0000000000005964.

[6] Ciccolallo L, Licitra L, Cantu G, Gatta G, Eurocare Working Group. Survival from salivary glands adenoid cystic carcinoma in European populations. Oral Oncol 2009;45:669–74. https://doi.org/10.1016/j.oraloncology.2008.10.010.

[7] American Cancer Society. Survival rates for salivary gland cancer. Available at: https://www.cancer.org/cancer/salivary-gland-cancer/detection-diagnosis-staging/survival-rates.html. Accessed August 11, 2021.

[8] Haderlein M, Scherl C, Semrau S, et al. High-grade histology as predictor of early distant metastases and decreased disease-free survival in salivary gland cancer irrespective of tumor subtype. Head Neck 2016;38(suppl 1):E2041–8. https://doi.org/10.1002/hed.24375.

[9] National Comprehensive Cancer Network (NCCN). NCCN clinical practice guidelines in Oncology (NCCN guidelines). Version 1 Head and neck cancers 2021. Available at: https://www.nccn.org/professionals/physician_gls/pdf/head-and-neck.pdf. [Accessed 7 December 2020].

[10] Licitra L, Cavina R, Grandi C, et al. Cisplatin, doxorubicin and cyclophosphamide in advanced salivary gland carcinoma. A phase II trial of 22 patients. Ann Oncol 1996;7:640–2. https://doi.org/10.1093/oxfordjournals.annonc.a010684.

[11] Airoldi M, Pedani F, Succo G, et al. Phase II randomized trial comparing vinorelbine versus vinorelbine plus cisplatin in patients with recurrent salivary gland malignancies. Cancer 2001;91:541–7. https://doi.org/10.1002/1097-0142(20010201)91:3<541::aid-cncr1032>3.0.co;2-y.

[12] Geiger JL, Ismaila N, Beadle B, et al. Management of salivary gland malignancy: ASCO guideline. J Clin Oncol 2021;39:1909–41. https://doi.org/10.1200/JCO.21.00449.

[13] Cohen RB, Delord JP, Doi T, et al. Pembrolizumab for the treatment of advanced salivary gland carcinoma: findings of the phase 1b KEYNOTE-028 study. Am J Clin Oncol 2018;41:1083–8. https://doi.org/10.1097/COC.0000000000000429.

[14] Marabelle A, Le DT, Ascierto PA, et al. Efficacy of pembrolizumab in patients with noncolorectal high microsatellite instability/mismatch repair-deficient cancer: results from the phase II KEYNOTE-158 study. J Clin Oncol 2020;38:1–10. https://doi.org/10.1200/JCO.19.02105.

[15] Marabelle A, Fakih M, Lopez J, et al. Association of tumour mutational burden with outcomes in patients with advanced solid tumours treated with pembrolizumab: prospective biomarker analysis of the multicohort, open-label, phase 2 KEYNOTE-158 study. Lancet Oncol 2020;21:1353–65. https://doi.org/10.1016/S1470-2045(20)30445-9.

[16] Fayette J, Even C, Digue L, et al. NISCAHN: a phase II, multicenter nonrandomized trial aiming at evaluating nivolumab (N) in two cohorts of patients (pts) with recurrent/metastatic (R/M) salivary gland carcinoma of the head and neck (SGCHN), on behalf of the Unicancer Head & Neck Group. J Clin Oncol 2019;37:6083. https://doi.org/10.1200/JCO.2019.37.15_suppl.6083.

[17] Tchekmedyian V, Sherman EJ, Dunn L, et al. A phase II trial cohort of nivolumab plus ipilimumab in patients (Pts) with recurrent/metastatic adenoid cystic carcinoma (R/M ACC). J Clin Oncol 2019;37:6084. https://doi.org/10.1200/JCO.2019.37.15_suppl.6084.

[18] Burman B, Sherman EJ, Dunn L, et al. A phase II trial cohort of nivolumab plus ipilimumab in patients (Pts) with recurrent/metastatic salivary gland cancers (R/M SGCs). J Clin Oncol 2021;39:6002. https://doi.org/10.1200/JCO.2021.39.15_suppl.6002.

[19] Papadopoulos KP, Lakhani N, Falchook GS, et al. Phase I, first-in-human trial of programmed cell death receptor-1 (PD-1) inhibitor, JTX-4014, in adult patients with advanced, refractory, solid tumors. Cancer Immunol Immunother 2021;70:763–72. https://doi.org/10.1007/s00262-020-02730-5.

[20] du Rusquec P, de Calbiac O, Robert M, Campone M, Frenel JS. Clinical utility of pembrolizumab in the management of advanced solid tumors: an evidence-based review on the emerging new data. Cancer Manag Res 2019;11:4297–312. https://doi.org/10.2147/CMAR.S151023.

[21] Reck M, Rodriguez-Abreu D, Robinson AG, et al. Pembrolizumab versus chemotherapy for PD-L1-positive non–small-cell lung cancer. N Engl J Med 2016;375:1823–33. https://doi.org/10.1056/NEJMoa1606774.

[22] Robert C, Schachter J, Long GV, et al. Pembrolizumab versus ipilimumab in advanced melanoma. N Engl J Med 2015;372:2521–32. https://doi.org/10.1056/NEJMoa1503093.