Supplementary Online Content

Shah MA, Kojima T, Hochhauser D, et al. Efficacy and Safety of pembrolizumab for heavily pretreated patients with advanced, metastatic adenocarcinoma or squamous cell carcinoma of the esophagus: the phase 2 KEYNOTE-180 study. *JAMA Oncol.* Published online December 20, 2018. doi:10.1001/jamaoncol.2018.5441

This supplementary material has been provided by the authors to give readers additional information about their work.

eAppendix. Methods

Patients

Male and female patients aged at least 18 years of age were eligible for enrollment if they had histologically confirmed advanced/metastatic adenocarcinoma or squamous cell carcinoma of the esophagus or advanced/metastatic Siewert type 1 adenocarcinoma of the gastroesophageal junction. In addition, patients had to have radiographic or clinical disease progression as confirmed by computed tomography scan on 2 previous lines of therapy; Eastern Cooperative Oncology Group performance status (ECOG PS) 0 or 1; life expectancy greater than 3 months; measurable disease per Response Evaluation Criteria in Solid Tumors version 1.1 by central imaging review (RECIST v1.1, central review); provide a newly obtained or archival tissue sample for biomarker assessment (central laboratory confirmation of tumor tissue sample adequacy was required before enrollment); and adequate organ function. Key exclusion criteria included prior treatment with a PD-1, PD-L1, or PD-L2 inhibitor; current participation and receipt of study treatment or participation in a clinical study within 4 weeks of first dose of study treatment; requirement for systemic steroids or other immunosuppressant therapy within 7 days of first dose of study treatment, history of or current non-infectious pneumonitis requiring steroids, and presence of active autoimmune disease and infections. All patients provided written, informed consent.

Outcomes

The primary endpoint was evaluation of the ORR per RECIST v1.1 by central review, defined as the proportion of patients in the analysis population with a complete response (CR) or partial response (PR). Responders include those with confirmed responses and those who did not yet have a confirmation scan. A patient with PR and then PD at the next scan was not included as a responder. Patients in the primary analysis population without ORR data were counted as non-responders. Secondary endpoints included evaluation of duration of response (DOR), defined as time from first CR or PR until PD or death, progression-free survival (PFS), defined as time from first day of study treatment until first documented PD (RECIST v1.1, central review) or death from any cause, overall survival, defined as time from first day of study treatment until death from any cause, safety and tolerability, and evaluation of PD-L1 immunohistochemistry in esophageal cancer and pembrolizumab efficacy. Non-responders were excluded from analysis of DOR. For PFS, patients with missing data were censored at last assessment. For OS, patients with missing data were censored at last know alive data. Patients were treated with pembrolizumab until confirmed PD by immune-related RECIST, unacceptable AEs, illness, study withdrawal, pregnancy, noncompliance with study

treatment, administrative reasons for up to 35 treatments, approximately 2 years. Patients who discontinued treatment for non-PD reasons had post-treatment follow-up until PD, initiation of a non-study cancer treatment, withdrawal of consent, or becoming lost to follow-up. All patients were followed by telephone contact for survival until death, withdrawal of consent, or death, whichever comes first. Adverse events were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 4. After treatment, adverse events were monitored for 30 days (serious AEs for 90 days).

Statistical Considerations

The planned sample size was approximately 100 patients. The table below shows the two sided 95% confidence interval of ORR with 100 patients for different observed response rates

Number of observed responders	ORR estimates	95% CI of ORR, %
17	17%	10.2-25.8
25	25%	16.9-34.7
30	30%	21.2-40.0
35	35%	25.7-45.2

Biomarker Analysis

PD-L1 expression in tumor and inflammatory cells in pre-treatment tumor tissue samples was characterized by immunohistochemistry (PD-L1 IHC 22C3 pharmDx, Agilent Technologies, Carpinteria, CA) using the combined positive score (CPS) defined as the number of PD-L1–positive cells (tumor cells, macrophages, lymphocytes) divided by the total number of tumor cells, multiplied by 100. KEYNOTE-180 data was used to determine a response-enriching PD-L1-positive cut-point alternative to CPS≥1 in patients with esophageal cancer. As such, using data from KEYNOTE-180, a CPS cutpoint of ≥10 versus <10 was identified to balance considerations related to positive predictive value (response rate in those above a cutpoint), sensitivity and prevalence based on evaluating the profile of response rate and prevalence as a function of cut-off and a receiver operating characteristic analysis (not shown). Patients with tumors scoring CPS ≥10 were defined as PD-L1 positive while those with tumors with CPS<10 were defined as PD-L1 negative.

eTable 1. Baseline Characteristics

Characteristics	**Pembrolizumab (N = 121)**
Median age, years (range)	65 (33 – 87)
≥65 years	64 (53)
Male, n (%)	100 (83)
M1 stage, n (%)	120 (99)
ECOG performance status, n (%)	
0	44 (36)
1	77 (64)
Geographic region, n (%)	
Asia	39 (32)
Non-Asia	82 (68)
Histological subtypes, n (%)	
Squamous cell carcinoma	63 (52)
Adenocarcinoma[a]	58 (48)
PD-L1 status, n (%)	
PD-L1 positive (CPS ≥10)	58 (48)
PD-L1 negative (CPS <10)	63 (52)
HER2 status[b], n (%)	
HER2 positive	13 (11)
HER2 negative	48 (40)
Unknown	47 (39)
Missing	13 (11)
Prior lines of therapy, n (%)	
2	106 (88)
≥3	15 (12)

[a]18 of the 58 (31%) patients with adenocarcinoma had Siewert type 1 adenocarcinoma of the esophageal gastric junction; [b]HER2 status was not required for patients with squamous cell carcinoma (three of these patients reported a negative HER2 status); CPS, combined positive score; ECOG, Eastern Cooperative Oncology Group; PD-L1, programmed death ligand 1

eTable 2. Antitumor Activity in Patients With Squamous Cell Carcinoma or Adenocarcinoma

	ESCC n = 63		**Adenocarcinoma n = 58**	
	n	**% (95% CI)**	**n**	**% (95% CI)**
Best response	**9**	**14 (7-25)**	**3**	**5 (1-14)**
DCR (CR+PR+SD)	25	40 (28-53)	12	21 (11-33)
Complete response	0	0	0	
Partial response	9	14 (7-25)	3	5 (1-14)
Stable disease	16	25 (15-38)	9	16 (7-27)
No assessment	4	6 (2-16)	9	16 (7-27)
Progressive disease	34	54 (41-67)	37	64 (50-76)
DOR, median (range), mo	NR (1.9+ to 14.4+)		NR (2.1 to 5.4+)	
PFS, median (95% CI), mo	2.1 (2.0-2.4)		1.9 (1.8-2.0)	
6-month PFS (95% CI), %	18 (9-28)		14 (6-24)	
9-month PFS (95% CI), %	12 (5-21)		7 (2-15)	
OS, median (95% CI), mo	6.8 (5.4-8.9)		3.9 (3.2-6.3)	
6-month OS (95% CI), %	57 (44-68)		40 (27-52)	
12-month OS (95% CI), %	34 (22-46)		22 (12-33)	

Abbreviations: DOR, duration of response; NR, not reached; OS, overall survival; PFS, progression-free survival; SCC, squamous cell carcinoma.

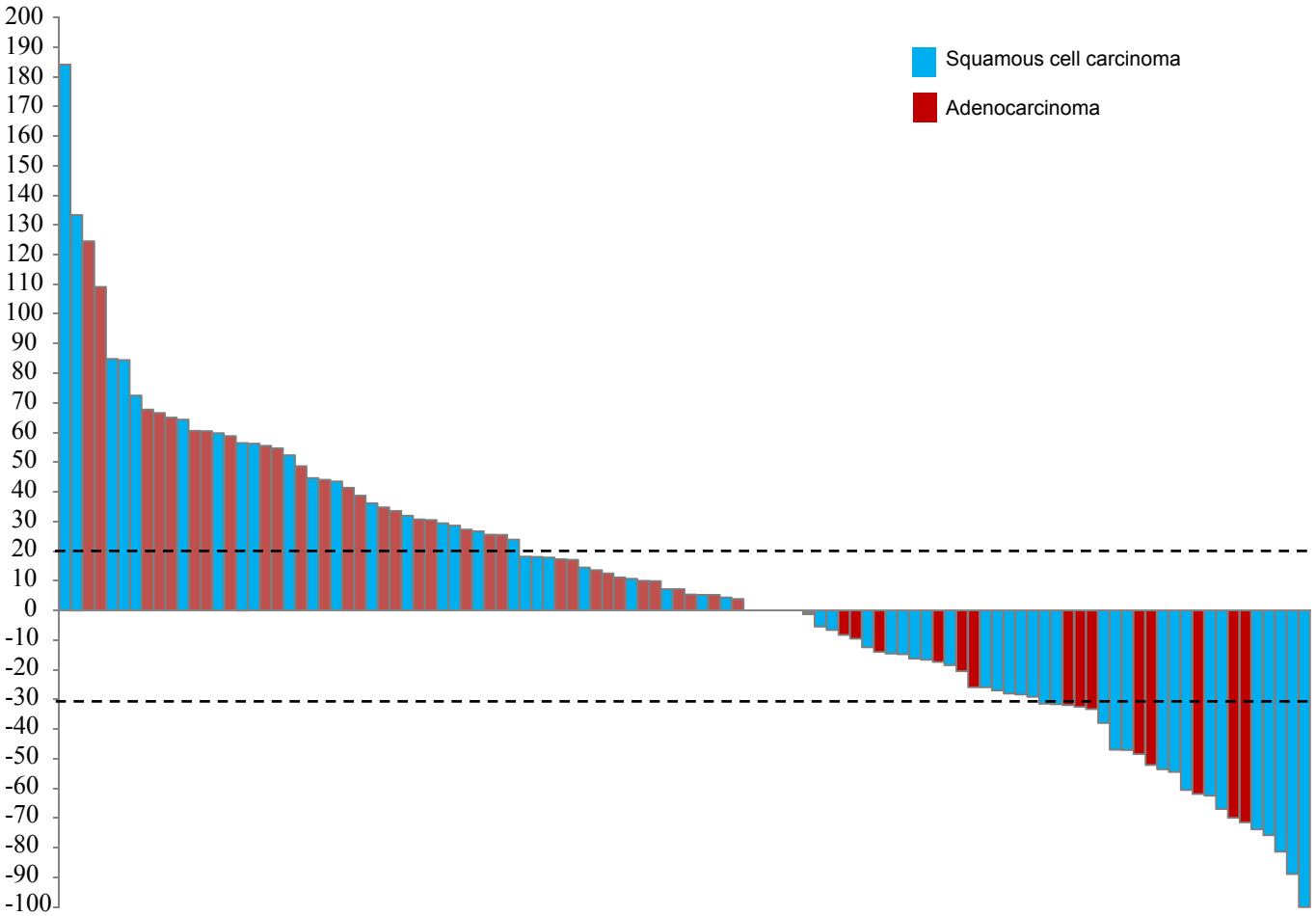
eTable 3. Antitumor Activity in Patients With PD-L1-Positive or PD-L1-Negative Tumors

	PD-L1-positive (CPS≥10) n = 58		**PD-L1-negative (CPS<10) n = 63**	
	n	**% (95% CI)**	**n**	**% (95% CI)**
Best response	**8**	**14 (6-25)**	**4**	**6 (2-16)**
DCR (CR+PR+SD)	21	36 (24-50)	16	25 (15-38)
Complete response	0	0	0	0
Partial response	8	14 (6-25)	4	6 (2-16)
Stable disease	13	22 (13-35)	12	19 (10-31)
NA	4	7 (2-17)	9	14 (7-25)
Progressive disease	33	57 (43-70)	38	60 (47-72)
DOR, median (range), mo	NR (1.9+ to 14.4+)		4.4 (2.1 to 5.3+)	
PFS, median (95% CI), mo	2.0 (1.9-2.2)		2.0 (1.9-2.1)	
6-month PFS (95% CI), %	22 (13-34)		10 (4-18)	
9-month PFS (95% CI), %	14 (7-25)		5 (1-12)	
OS, median (95% CI), mo	6.3 (4.4-9.3)		5.4 (3.9-6.3)	
6-month OS (95% CI), %	52 (38-64)		46 (33-58)	
12-month OS (95% CI), %	35 (23-47)		22 (12-33)	

eTable 4. Grade 3-5 Treatment-Related Adverse Events

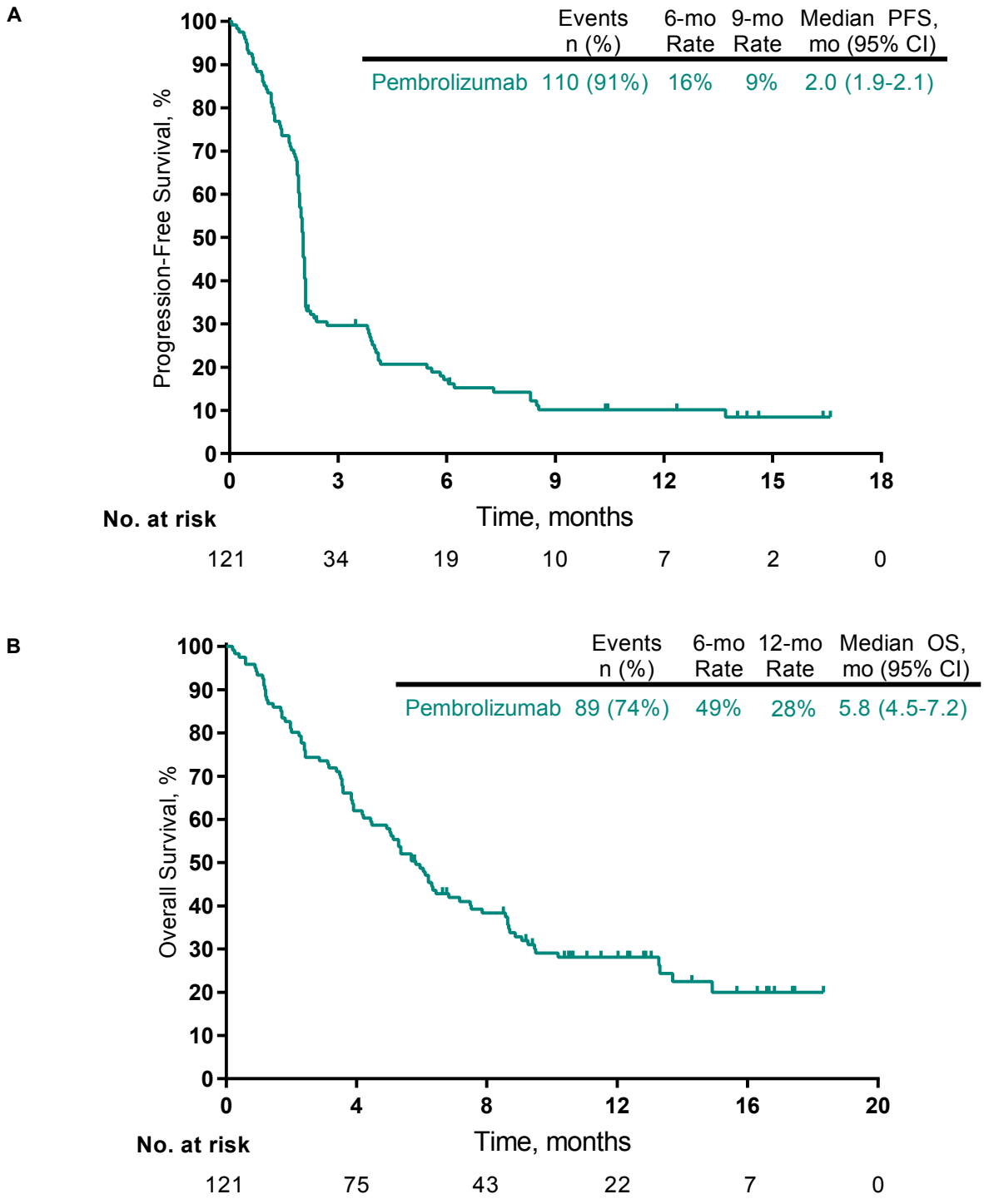
Treatment-related AEs, n (%)	**N = 121**	
	Grade 3-4	**Grade 5**
All	14 (11)	1 (1)
Type 1 diabetes mellitus	4 (3)	0
Pneumonitis	2 (2)	1 (1)
Hypophysitis	1 (1)	0
Thyroiditis	1 (1)	0
Diarrhea	1 (1)	0
Pancreatitis	1 (1)	0
Asthenia	1 (1)	0
Malaise	1 (1)	0
Herpes zoster	1 (1)	0
Pneumonia	1 (1)	0
Alanine aminotransferase increased	1 (1)	0
Blood alkaline phosphatase increased	1 (1)	0
Hyperkalemia	1 (1)	0
Hyperglycemia	1 (1)	0
Arthralgia	1 (1)	0
Nephritis	1 (1)	0
Chronic obstructive pulmonary disease	1 (1)	0
Embolism	1 (1)	0

eFigure 1. Best Percentage Change From Baseline in Target Lesion Size (RECIST v1.1, Central Review)



Response was assessed per Response Evaluation Criteria in Solid Tumors (RECIST) version 1..1 by central review at baseline and after at least 1 postbaseline tumor assessment. Best change from baseline in confirmed responders with squamous cell carcinoma or adenocarcinoma histology

eFigure 2. Survival Outcomes in all Patients



(A) Progression-free survival assessed per RECIST version 1.1 by central review) and (B) Overall survival