Supplementary data

Supplementary methods

Study procedures and assessments

Confirmatory imaging assessments were performed ≥4 weeks after initial documentation of all responses. Unconfirmed responses were considered stable disease for the best overall response assessment. For externally visible target lesions in patients with locally advanced cutaneous squamous cell carcinoma, a complete response determined by digital medical photography was required to be confirmed by biopsies.

Statistical analysis

Following analysis of conventional imaging to determine the primary endpoint, exploratory 18 F-fluorodeoxyglucose (FDG) positron emission tomography (PET) analysis using European Organisation for Research and Treatment of Cancer PET criteria was performed on up to five target lesions per patient.[1] Target lesions were metabolically hyperactive at baseline (standardized uptake value [SUV] ≥2) and ≥20 mm in diameter. Complete metabolic response was defined as the disappearance of all metabolically hyperactive target lesions. Partial metabolic response was defined as a >25% reduction in summed maximum SUV from baseline. Stable metabolic disease was defined as a ≤25% increase in summed maximum SUV from baseline and a ≤20% increase in the sum of diameters from baseline, while not meeting the definition for progressive metabolic disease. To meet the defined criteria for complete or partial metabolic responses and stable metabolic disease, no new lesions of FDG uptake could be observed compared with the baseline scan. Progressive metabolic disease was defined as a >25% increase in summed maximum SUV or a >20% increase in sum of diameters from baseline, and

the appearance of new lesions compared with baseline scan.

Programmed cell death-ligand 1 (PD-L1) levels were expressed as a tumor proportion score, defined as the percentage of tumor cells with detectable PD-L1 membrane staining by immunohistochemistry. Evaluating coding regions of targeted genes, tumor mutational burden was calculated as the number of somatic single nucleotide variants, insertions, and deletions per megabase of genomic sequence analyzed.

46 ## Reference

47 1. Young H, Baum R, Cremerius U*, et al.* Measurement of clinical and subclinical
48 tumour response using [18F]-fluorodeoxyglucose and positron emission
49 tomography: review and 1999 EORTC recommendations. European
50 Organization for Research and Treatment of Cancer (EORTC) PET Study
51 Group. *Eur J Cancer* 1999;35:1773-82.

52 **Table S1. Tumor response per independent central review by PD-L1 status**

	PD-L1 <1% (n=10)	PD-L1 ≥1% (n=31)	PD-L1 ≥1–<5% (n=11)	PD-L1 ≥5–<50% (n=11)	PD-L1 ≥50% (n=9)	PD-L1 not evaluable* (n=22)
Objective response, n (%; 95% CI)[†]	4 (40; 12.2–73.8)	22 (71; 52.0–85.8)	8 (73; 39.0–94.0)	9 (82; 48.2–97.7)	5 (56; 21.2–86.3)	13 (59; 36.4–79.3)
Best overall response, n (%)						
Complete response	1 (10)	10 (32)	3 (27)	4 (36)	3 (33)	3 (14)
Partial response	3 (30)	12 (39)	5 (46)	5 (46)	2 (22)	10 (46)
Stable disease	3 (30)	3 (10)	1 (9)	1 (9)	1 (11)	1 (5)
Progressive disease	1 (10)	5 (16)	2 (18)	1 (9)	2 (22)	3 (14)
Not evaluable[‡]	1 (10)	0	0	0	0	4 (18)
Disease control, n (%; 95% CI)	8 (80; 44.4–97.5)	26 (84; 66.3–94.5)	9 (82; 48.2–97.7)	10 (91; 58.7–99.8)	7 (78; 40.0–97.2)	15 (68; 45.1–86.1)
Durable disease control, n (%; 95% CI)[§]	7 (70; 34.8–93.3)	26 (84; 66.3–94.5)	9 (82; 48.2–97.7)	10 (91; 58.7–99.8)	7 (78; 40.0–97.2)	15 (68; 45.1–86.1)

53 Data cut-off date: April 20, 2022.

54 *PD-L1 status unknown due to sample viability. Slides from 30 patients were excluded from PD-L1 immunohistochemistry analysis because the slides expired (>6 months after

55 slide cut date) or because there was an insufficient number of viable cells (<100) on the slide.

56 [†]Clopper-Pearson exact CI.

[‡]Not evaluable includes missing and unknown tumor responses.

[§]Proportion of patients with response for 105 days without progressive disease.

CI, confidence interval; PD-L1, programmed cell death-ligand 1.

Table S2. Treatment-related AEs

	Advanced CSCC (Group 4, n=63)	
Patients, n (%)	**Any grade**	**Grade ≥3**
Any treatment-related AE	52 (83)	10 (16)
Any serious treatment-related AE	10 (16)	6 (10)
Treatment-related AE leading to discontinuation	7 (11)	5 (8)
Treatment-related AE leading to death	1 (2)	1 (2)
Most common treatment-related AEs*		
Pruritus	14 (22)	0 (0)
Fatigue	11 (18)	0 (0)
Rash	11 (18)	0 (0)
Maculopapular rash	8 (13)	1 (2)
Arthralgia	8 (13)	0 (0)
Dermatitis	7 (11)	0 (0)

Data cut-off date: April 20, 2022.

*Treatment-related AEs reported in >10% of patients, ordered by frequency of any grade.

AE, adverse event; CSCC, cutaneous squamous cell carcinoma.

Table S3. Investigator-assessed immune-related AEs

	Advanced CSCC (Group 4, n=63)	
Patients, n (%)	**Any grade**	**Grade ≥3**
Any immune-related AE	48 (76)	10 (16)
Any serious immune-related AE	9 (14)	6 (10)
Immune-related AE leading to discontinuation	7 (11)	5 (8)
Immune-related AE leading to death	1 (2)	1 (2)
Most common immune-related AEs*		
Pruritus	14 (22)	0 (0)
Rash	10 (16)	0 (0)
Fatigue	9 (14)	0 (0)
Maculopapular rash	8 (13)	1 (2)
Arthralgia	8 (13)	0 (0)
Dermatitis	7 (11)	0 (0)

Data cut-off date: April 20, 2022.

*Immune-related AEs reported in >10% of patients, ordered by frequency of any grade.

AE, adverse event; CSCC, cutaneous squamous cell carcinoma.

Table S4. Comparison of treatment-emergent and treatment-related AEs between Group 4 and Groups 1, 2, and 3

Patients, n (%)	Groups 1, 2, and 3 (n=193)	Group 4 (n=63)
Any treatment-emergent AE	192 (100)	63 (100)
Grade ≥3 treatment-emergent AEs	95 (49)	34 (54)
Any treatment-related AE	148 (77)	52 (83)
Grade ≥3 treatment-related AEs	33 (17)	10 (16)
Treatment-emergent AEs leading to treatment discontinuation	19 (10)	11 (18)
Treatment-emergent AEs leading to death	5 (3)	6 (10)
Treatment-related AEs leading to treatment discontinuation	16 (8)	7 (11)
Treatment-related AEs leading to death	1 (1)	1 (2)

AE, adverse event.

.

Table S5. Tumor response assessment per independent central review and investigator assessment as measured by conventional imaging and FDG-PET imaging (primary analysis)*

	Conventional imaging (primary endpoint, n=63)†			FDG-PET imaging (exploratory endpoint, n=55)	
Endpoint	**Independent central review**	**Investigator assessment**	**Endpoint**	**Independent central review**	**Investigator assessment**
ORR, n (%)	37 (58.7)	37 (58.7)	ORR, n (%)	34 (61.8)	38 (69.1)
95% CI‡	45.6–71.0	45.6–71.0	95% CI‡	47.7–74.6	55.2–80.9
Complete response	11 (17.5)	8 (12.7)	Complete metabolic response	14 (25.5)	16 (29.1)
Partial response	26 (41.3)	29 (46.0)	Partial metabolic response	20 (36.4)	22 (40.0)
Stable disease	9 (14.3)	9 (14.3)	Stable metabolic disease	5 (9.1)	2 (3.6)
Non-complete response/non-progressive disease	3 (4.8)	—	—	—	—
Progressive disease	9 (14.3)	11 (17.5)	Progressive metabolic disease	3 (5.5)	2 (3.6)
Not evaluable§	5 (7.9)	6 (9.5)	Not evaluable§	13 (23.6)	13 (23.6)

*Data cut-off date: April 20, 2020.

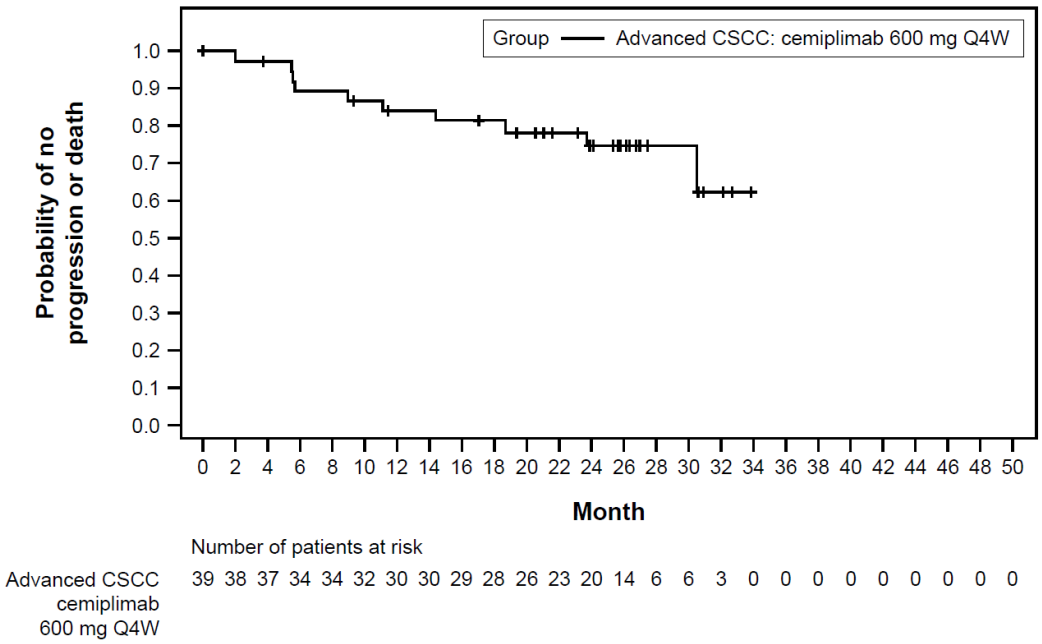
†The primary endpoint of ORR by conventional imaging was established before reviewing FDG-PET images as an exploratory endpoint.

‡Clopper-Pearson exact CI.

§Includes missing and unknown tumor response.

CI, confidence interval; FDG-PET, ^{18}F-fluorodeoxyglucose positron emission tomography; ORR, objective response rate.

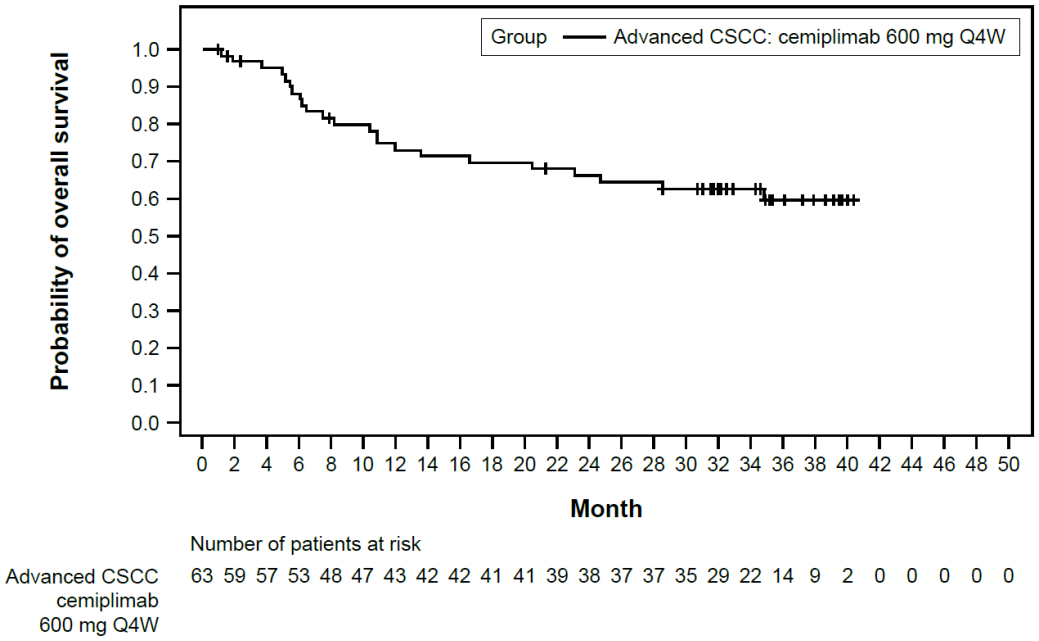
Figure S1. Duration of response in advanced CSCC, Group 4



Data cut-off date: April 20, 2022.

CSCC, cutaneous squamous cell carcinoma; Q4W, every 4 weeks.

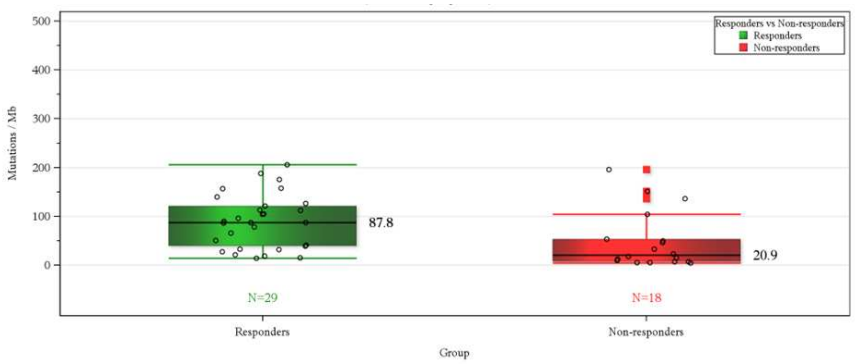
Figure S2. Overall survival in advanced CSCC, Group 4



Data cut-off date: April 20, 2022.

CSCC, cutaneous squamous cell carcinoma; Q4W, every 4 weeks.

Figure S3. Association between tumor mutational burden and best overall response per independent central review



Data cut-off date: April 20, 2022.

Black lines in each box denote the median; lower and upper boundaries of box denote the IQR; and upper and lower whiskers indicate maximum and minimum values. Individual patients are indicated by open black circles. Open black circles beyond the whiskers are outliers. Closed red boxes are duplicates of the outliers.

IQR, interquartile range.