Supplementary Table 1. Baseline Scores and Change from Baseline (MMRM) in Patients in the Full Analysis Set who had Baseline and Post-Baseline Assessments on each QLQ-C30 Scale or Item

QLQ-C30 scale/item	Baseline, mean ± SD (n)	LS mean change ± SE (n)	
		Cycle 3	Cycle 12
Global Health Status/HRQoL	65.1 ± 22.9 (150)	7.8 ± 1.6 (122)**	**11.1 ± 2.6 (43)****
Functioning scales†			
Physical function	80.1 ± 22.8 (151)	1.1 ± 1.3 (124)	4.0 ± 2.1 (43)
Role function	75.8 ± 30.0 (151)	0.4 ± 2.1 (123)	5.6 ± 3.4 (43)
Emotional function	80.2 ± 21.2 (151)	4.2 ± 1.3 (123)*	5.3 ± 2.2 (43)*
Cognitive function	83.4 ± 22.2 (151)	1.7 ± 1.4 (123)	2.5 ± 2.3 (43)
Social function	74.4 ± 31.8 (150)	5.3 ± 1.8 (122)*	8.6 ± 3.0 (43)*
Symptoms‡			
Fatigue	30.2 ± 24.6 (152)	–2.8 ± 1.7 (125)	–4.8 ± 2.8 (43)
Nausea/vomiting	4.6 ± 12.2 (152)	–1.6 ± 0.8 (125)*	–2.9 ± 1.3 (43)*
Pain	29.8 ± 30.4 (152)	**–11.5 ± 1.9 (125)****	**–14.3 ± 3.1 (43)****
Dyspnea	12.9 ± 23.4 (152)	0.7 ± 1.7 (125)	1.5 ± 2.9 (43)
Insomnia	27.4 ± 28.0 (151)	–9.1 ± 2.0 (123)**	**–17.4 ± 3.3 (43)****
Appetite loss	19.5 ± 29.3 (152)	–8.4 ± 1.6 (124)**	**–13.7 ± 2.7 (43)****
Constipation	13.6 ± 24.1 (152)	–4.5 ± 1.5 (125)*	**–11.2 ± 2.5 (43)****
Diarrhea	4.9 ± 13.6 (150)	3.6 ± 1.4 (121)*	0.6 ± 2.3 (43)
Financial difficulty	19.1 ± 30.7 (150)	0.5 ± 2.0 (122)	–3.4 ± 3.3 (43)

*p<0.05 and **p<0.001 versus baseline. †Higher scores reflect better outcomes. ‡Lower scores reflect better outcomes.

The questionnaire was administered on day 1 of each treatment cycle (treatment cycle defined as 8 weeks for Groups 1 and 2 and 9 weeks for Group 3).

HRQoL, health-related quality of life; LS, least squares; MMRM, mixed-effects repeated measures models; QLQ-C30, European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire; SD, standard deviation; SE, standard error.

Supplementary Table 2. Treatment-Emergent Adverse Events

	Advanced CSCC (N=193)	
n (%)	**Any grade**	**Grade ≥3**
Any TEAE	192 (99.5)	94 (48.7)
TEAEs leading to discontinuation	19 (9.8)	14 (7.3)
TEAEs of any grade reported in ≥10% of patients or Grade ≥3 TEAEs reported in at least one patient[†]		
Fatigue	67 (34.7)	5 (2.6)
Diarrhea	53 (27.5)	2 (1.0)
Nausea	46 (23.8)	0
Pruritus	41 (21.2)	0
Cough	32 (16.6)	0
Rash[‡]	32 (16.6)	1 (0.5)
Arthralgia	28 (14.5)	1 (0.5)
Constipation	26 (13.5)	1 (0.5)
Vomiting	24 (12.4)	1 (0.5)
Actinic keratosis	23 (11.9)	0
Maculopapular rash[‡]	23 (11.9)	1 (0.5)
Anemia	22 (11.4)	8 (4.1)
Hypothyroidism	22 (11.4)	0
Headache	21 (10.9)	0
Upper respiratory tract infection	20 (10.4)	0
Abdominal pain	17 (8.8)	1 (0.5)
Basal cell carcinoma	15 (7.8)	3 (1.6)
Dizziness	15 (7.8)	1 (0.5)
Dyspnea	15 (7.8)	3 (1.6)
Fall	15 (7.8)	3 (1.6)
Urinary tract infection	15 (7.8)	3 (1.6)

Wound infection	15 (7.8)	2 (1.0)
Hypertension	14 (7.3)	9 (4.7)
Increased blood creatine	14 (7.3)	1 (0.5)
Pain in extremity	14 (7.3)	2 (1.0)
Cellulitis	13 (6.7)	8 (4.1)
Hypokalemia	13 (6.7)	3 (1.6)
Pneumonitis	13 (6.7)	5 (2.6)
Increased aspartate aminotransferase	12 (6.2)	1 (0.5)
Skin infection	12 (6.2)	3 (1.6)
Hyperuricemia	10 (5.2)	1 (0.5)
Squamous cell carcinoma of skin	10 (5.2)	3 (1.6)
Dysphagia	9 (4.7)	2 (1.0)
Musculoskeletal pain	9 (4.7)	2 (1.0)
Pneumonia	9 (4.7)	7 (3.6)
Dehydration	8 (4.1)	3 (1.6)
Depression	8 (4.1)	2 (1.0)
Hyperglycemia	8 (4.1)	4 (2.1)
Hypotension	8 (4.1)	1 (0.5)
Neck pain	8 (4.1)	2 (1.0)
Atrial fibrillation	6 (3.1)	1 (0.5)
Delirium	6 (3.1)	1 (0.5)
Hypercalcemia	6 (3.1)	3 (1.6)
Hyponatremia	6 (3.1)	3 (1.6)
Squamous cell carcinoma	6 (3.1)	2 (1.0)
Colitis	5 (2.6)	2 (1.0)
Decreased lymphocyte count	5 (2.6)	1 (0.5)
Hematuria	5 (2.6)	2 (1.0)
Lymphopenia	5 (2.6)	3 (1.6)
Muscular weakness	5 (2.6)	2 (1.0)

Pleural effusion	5 (2.6)	2 (1.0)
Sepsis	5 (2.6)	5 (2.6)
Tumor pain	5 (2.6)	1 (0.5)
Acute kidney injury	4 (2.1)	1 (0.5)
Decreased platelet count	4 (2.1)	1 (0.5)
Deep vein thrombosis	4 (2.1)	2 (1.0)
Hypoglycemia	4 (2.1)	1 (0.5)
Pain	4 (2.1)	1 (0.5)
Tumor hemorrhage	4 (2.1)	1 (0.5)
Autoimmune hepatitis	3 (1.6)	3 (1.6)
Confusional state	3 (1.6)	1 (0.5)
Hypophosphatemia	3 (1.6)	2 (1.0)
Increased international normalized ratio	3 (1.6)	1 (0.5)
Influenza	3 (1.6)	1 (0.5)
Polyarthritis	3 (1.6)	1 (0.5)
Soft tissue infection	3 (1.6)	1 (0.5)
Staphylococcal infection	3 (1.6)	1 (0.5)
Syncope	3 (1.6)	3 (1.6)
B-cell lymphoma	2 (1.0)	2 (1.0)
Breast cancer	2 (1.0)	2 (1.0)
Catheter site infection	2 (1.0)	1 (0.5)
Death[§]	2 (1.0)	2 (1.0)
Decreased neutrophil count	2 (1.0)	1 (0.5)
Fungal skin infection	2 (1.0)	1 (0.5)
Gastroenteritis	2 (1.0)	1 (0.5)
Hip fracture	2 (1.0)	2 (1.0)
Increased weight	2 (1.0)	1 (0.5)
Myocardial infarction	2 (1.0)	2 (1.0)
Esophagitis	2 (1.0)	1 (0.5)

Peripheral swelling	2 (1.0)	1 (0.5)
Pneumonia aspiration	2 (1.0)	1 (0.5)
Postoperative wound infection	2 (1.0)	1 (0.5)
Presyncope	2 (1.0)	1 (0.5)
Psoriasis	2 (1.0)	1 (0.5)
Pulmonary embolism	2 (1.0)	2 (1.0)
Urinary retention	2 (1.0)	1 (0.5)
Wound complication	2 (1.0)	1 (0.5)
Acute respiratory distress syndrome	1 (0.5)	1 (0.5)
Acute respiratory failure	1 (0.5)	1 (0.5)
Adjustment disorder	1 (0.5)	1 (0.5)
Angina pectoris	1 (0.5)	1 (0.5)
Arterial hemorrhage	1 (0.5)	1 (0.5)
Aseptic meningitis	1 (0.5)	1 (0.5)
Atopic dermatitis	1 (0.5)	1 (0.5)
Autoimmune dermatitis	1 (0.5)	1 (0.5)
Cardiogenic shock	1 (0.5)	1 (0.5)
Cerebral infarction	1 (0.5)	1 (0.5)
Cholecystitis	1 (0.5)	1 (0.5)
Chronic obstructive pulmonary disease	1 (0.5)	1 (0.5)
Clostridium difficile colitis	1 (0.5)	1 (0.5)
Complete atrioventricular block	1 (0.5)	1 (0.5)
Decreased white blood cell count	1 (0.5)	1 (0.5)
Device related infection	1 (0.5)	1 (0.5)
Duodenal ulcer	1 (0.5)	1 (0.5)
Encephalitis	1 (0.5)	1 (0.5)
Erysipelas	1 (0.5)	1 (0.5)
Extradural abscess	1 (0.5)	1 (0.5)
Facial neuralgia	1 (0.5)	1 (0.5)

Fungating wound	1 (0.5)	1 (0.5)
Groin infection	1 (0.5)	1 (0.5)
Hematemesis	1 (0.5)	1 (0.5)
Hepatitis	1 (0.5)	1 (0.5)
Hypertensive crisis	1 (0.5)	1 (0.5)
Hypophysitis	1 (0.5)	1 (0.5)
Increased lipase	1 (0.5)	1 (0.5)
Influenza pneumonia	1 (0.5)	1 (0.5)
Limb abscess	1 (0.5)	1 (0.5)
Myocarditis	1 (0.5)	1 (0.5)
Nasal cavity cancer	1 (0.5)	1 (0.5)
Optic atrophy	1 (0.5)	1 (0.5)
Osteomyelitis	1 (0.5)	1 (0.5)
Pancytopenia	1 (0.5)	1 (0.5)
Pericarditis	1 (0.5)	1 (0.5)
Positive influenza A virus test	1 (0.5)	1 (0.5)
Proctitis	1 (0.5)	1 (0.5)
Psoas abscess	1 (0.5)	1 (0.5)
Pulmonary edema	1 (0.5)	1 (0.5)
Radius fracture	1 (0.5)	1 (0.5)
Renal cell carcinoma	1 (0.5)	1 (0.5)
Respiratory failure	1 (0.5)	1 (0.5)
Septic shock	1 (0.5)	1 (0.5)
Small intestinal hemorrhage	1 (0.5)	1 (0.5)
Small intestinal obstruction	1 (0.5)	1 (0.5)
Soft tissue necrosis	1 (0.5)	1 (0.5)
Subdural hematoma	1 (0.5)	1 (0.5)
Suicidal ideation	1 (0.5)	1 (0.5)
Urinary tract obstruction	1 (0.5)	1 (0.5)

[†]Ordered by frequency of adverse events of any grade.

[‡]Although rash and maculopapular rash might reflect the same condition, they were listed as two distinct events for the safety report of the study.

[§]The two patients with AE term of death, and other patients who experienced TEAEs leading to death have been previously reported, and there have been no new fatal AEs since those reports (Migden *NEJM* 2018, Migden *Lancet Oncol* 2020, Rischin *JITC* 2020).[1-3]

AE, adverse event; CSCC, cutaneous squamous cell carcinoma; TEAE, treatment-emergent AE.

Supplementary Table 3. Treatment-Related Adverse Events Reported in ≥5% of Patients from the Phase 2 Study

	Patients with advanced CSCC (N=193)	
n (%)	**Any grade**	**Grade ≥3**
Any TRAE	148 (76.7)	33 (17.1)
TRAEs of any grade reported in ≥5% of patients or Grade ≥3 TRAEs reported in at least one patient[†]		
Fatigue	40 (20.7)	1 (0.5)
Pruritus	29 (15.0)	0
Diarrhea	24 (12.4)	2 (1.0)
Rash[‡]	23 (11.9)	1 (0.5)
Hypothyroidism	21 (10.9)	0
Maculopapular rash[‡]	21 (10.9)	1 (0.5)
Nausea	18 (9.3)	0
Pneumonitis	13 (6.7)	5 (2.6)
Arthralgia	12 (6.2)	0
Increased alanine aminotransferase	12 (6.2)	0
Increased aspartate aminotransferase	11 (5.7)	1 (0.5)
Colitis	5 (2.6)	2 (1.0)
Dizziness	5 (2.6)	1 (0.5)
Vomiting	5 (2.6)	2 (1.0)
Anemia	4 (2.1)	2 (1.0)
Autoimmune hepatitis	3 (1.6)	3 (1.6)
Hypokalemia	3 (1.6)	1 (0.5)
Polyarthritis	3 (1.6)	1 (0.5)
Decreased lymphocyte count	2 (1.0)	1 (0.5)
Decreased neutrophil count	2 (1.0)	1 (0.5)
Decreased platelet count	2 (1.0)	1 (0.5)

Neck pain	2 (1.0)	1 (0.5)
Psoriasis	2 (1.0)	1 (0.5)
Autoimmune dermatitis	1 (0.5)	1 (0.5)
Aseptic meningitis	1 (0.5)	1 (0.5)
B-cell lymphoma	1 (0.5)	1 (0.5)
Confusional state	1 (0.5)	1 (0.5)
Death[§]	1 (0.5)	1 (0.5)
Decreased white blood cell count	1 (0.5)	1 (0.5)
Duodenal ulcer	1 (0.5)	1 (0.5)
Encephalitis	1 (0.5)	1 (0.5)
Esophagitis	1 (0.5)	1 (0.5)
Gastroenteritis	1 (0.5)	1 (0.5)
Hepatitis	1 (0.5)	1 (0.5)
Hypophosphatemia	1 (0.5)	1 (0.5)
Hypophysitis	1 (0.5)	1 (0.5)
Increased lipase	1 (0.5)	1 (0.5)
Myocarditis	1 (0.5)	1 (0.5)
Pericarditis	1 (0.5)	1 (0.5)
Pneumonia	1 (0.5)	1 (0.5)
Proctitis	1 (0.5)	1 (0.5)
Small intestinal hemorrhage	1 (0.5)	1 (0.5)

[†]Ordered by frequency of any grade.

[‡]Although rash and maculopapular rash might reflect the same condition, they were listed as two distinct events for the safety report of the study.

CSCC, cutaneous squamous cell carcinoma; TRAE, treatment-related adverse event.

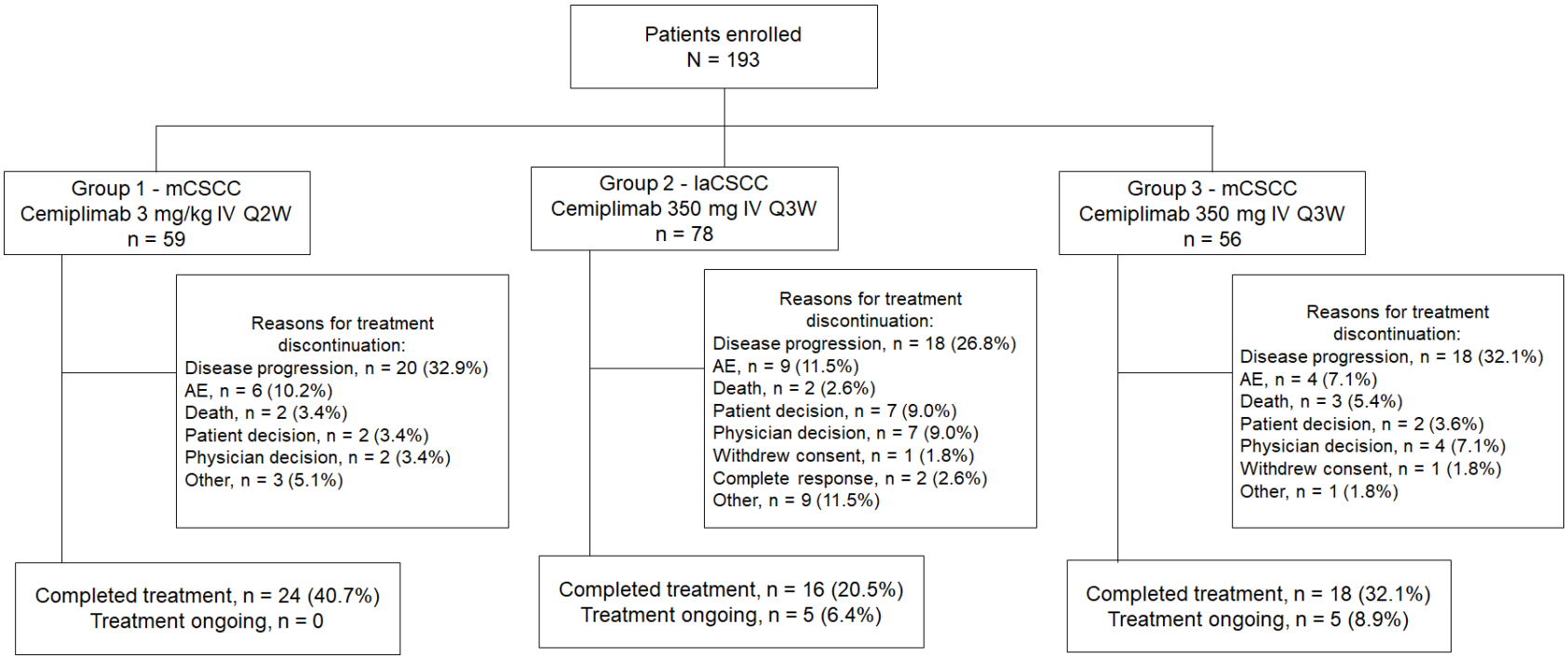
Supplementary Table 4. Immune-Related Adverse Events Based on Sponsor-Provided List

	Patients with advanced CSCC (N=193)	
n (%)	**Any grade**	**Grade ≥3**
Any irAE	57 (29.5)	18 (9.3)
irAEs of any grade reported in ≥5% of patients or Grade ≥3 irAEs reported in at least one patient[†]		
Hypothyroidism	21 (10.9)	0
Pneumonitis	12 (6.2)	5 (2.6)
Diarrhea	4 (2.1)	2 (1.0)
Colitis	3 (1.6)	1 (0.5)
Autoimmune hepatitis	2 (1.0)	2 (1.0)
Polyarthritis	2 (1.0)	1 (0.5)
Rash	2 (1.0)	1 (0.5)
Aseptic meningitis	1 (0.5)	1 (0.5)
Autoimmune dermatitis	1 (0.5)	1 (0.5)
Encephalitis	1 (0.5)	1 (0.5)
Hepatitis	1 (0.5)	1 (0.5)
Hypophysitis	1 (0.5)	1 (0.5)
Increase aspartate aminotransferase	1 (0.5)	1 (0.5)
Myocarditis	1 (0.5)	1 (0.5)
Pericarditis	1 (0.5)	1 (0.5)

[†]Ordered by frequency of any grade.

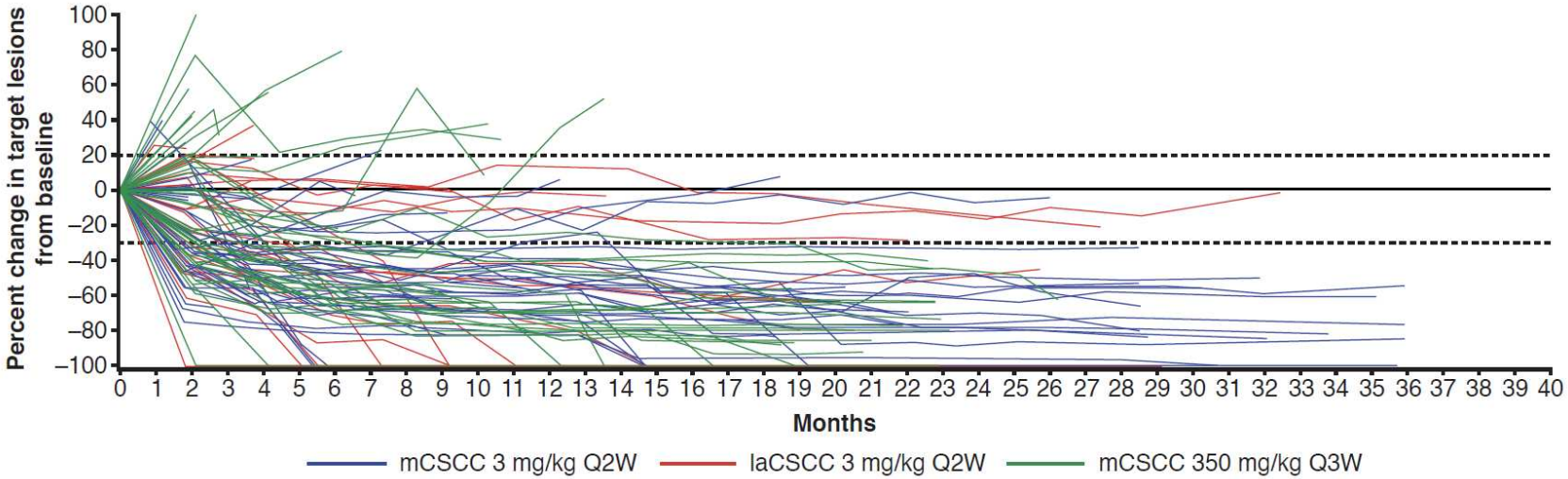
CSCC, cutaneous squamous cell carcinoma; irAE, immune-related adverse event.

Supplementary Figure 1. Patient Disposition in the Phase 2 Study



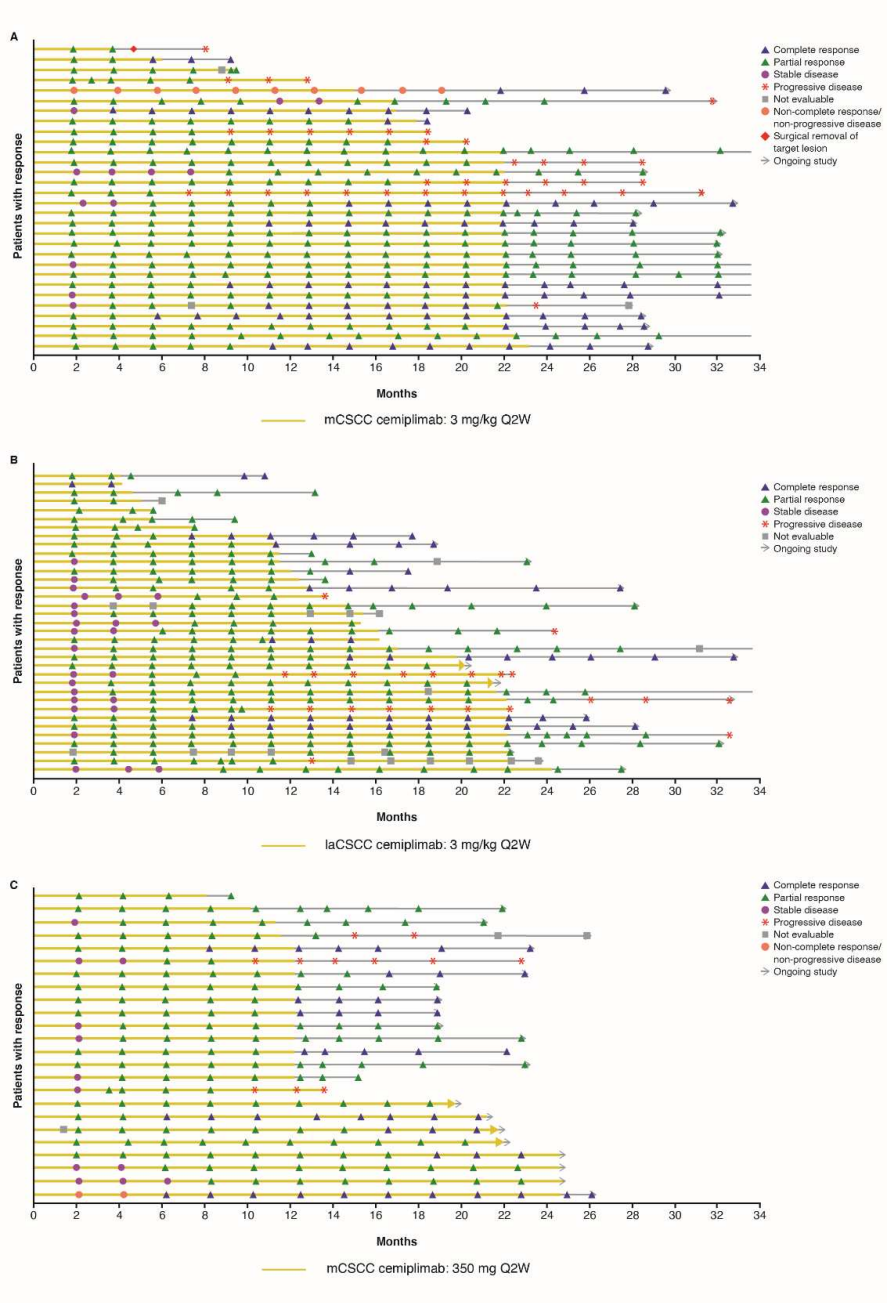
AE, adverse event; IV, intravenous; laCSCC, locally advanced cutaneous squamous cell carcinoma; mCSCC, metastatic cutaneous squamous cell carcinoma; Q2W, every 2 weeks; Q3W, every 3 weeks.

Supplementary Figure 2. Percent Change in Target Lesions from Baseline per RECIST 1.1 per Independent Central Review



laCSCC, locally advanced cutaneous squamous cell carcinoma; mCSCC, metastatic cutaneous squamous cell carcinoma; RECIST 1.1, Response Evaluation Criteria in Solid Tumors version 1.1; Q2W, every 2 weeks; Q3W, every 3 weeks.

Supplementary Figure 3. Tumor Response in a) mCSCC Receiving Cemiplimab 3 mg/kg Q2W (Group 1), b) laCSCC Receiving Cemiplimab 3 mg/kg Q2W (Group 2), and c) mCSCC Receiving Cemiplimab 350 mg/kg Q3W (Group 3)



laCSCC, locally advanced cutaneous squamous cell carcinoma; mCSCC, metastatic cutaneous squamous cell carcinoma; Q2W, every 2 weeks; Q3W, every 3 weeks.

References

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