Clinical and patient-reported outcomes (PROs) in C-POST: A phase 3 trial of adjuvant cemiplimab versus placebo for high-risk cutaneous squamous cell carcinoma (CSCC)

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SYNOPSIS

- There is an unmet need among patients with CSCC who are at high risk of disease recurrence after surgery and adjuvant radiotherapy; there are no adjuvant systemic therapy options with proven benefit.[1]
- The C-POST trial (NCT03969004) evaluated cemiplimab as adjuvant therapy for the treatment of patients at high risk of CSCC recurrence after surgery and radiation therapy.[2]
- Clinical and PRO data from this study support adjuvant cemiplimab as a potential new standard of care for patients at high risk of CSCC recurrence.

OBJECTIVE

- To report the efficacy, safety, and PROs of adjuvant cemiplimab in patients at high risk of CSCC recurrence after surgery and radiation therapy from the C-POST trial.

METHODS

- High risk was defined by the presence of ≥1 nodal and/or non-nodal disease criterion (**Figure 1**).
- Patients with CSCC at high risk of recurrence after surgery and radiation therapy were randomized 1:1 to adjuvant cemiplimab (n=209) or placebo (n=206) (**Supplementary Figure 1**).
  - Dosing was cemiplimab 350 mg or placebo Q3W for approximately 12 weeks, followed by cemiplimab 700 mg or placebo Q6W for 36 weeks for a total planned treatment duration of 48 weeks (4 cycles; cycle length=12 weeks).
- Key inclusion criteria included: high-risk CSCC, defined by ≥1 high-risk category; macroscopic gross resection of all pathologically confirmed CSCC disease; completion of post-operative radiation therapy (≥50 Gy biologically equivalent dose) within 2–10 weeks of randomization; Eastern Cooperative Oncology Group performance status of 0 or 1; and adequate hepatic, renal, and bone marrow function.
- Key exclusion criteria are summarized in the **Supplementary Methods**.

Figure 1. Nodal and non-nodal high-risk criteria† for study inclusion

Nodal disease	In-transit metastases	Perineural invasion	T4 lesions	Recurrent CSCC
ECE with ≥1 node ≥20 mm OR ≥3 nodes regardless of ECE	Skin or subcutaneous metastases >20 mm from the primary lesion but not beyond the regional nodal basin	Clinical and/or radiologic involvement of named nerves	Invasion of cortical bone or skull base	CSCC that arises within the area of previously resected tumor, plus ≥1 additional feature: • ≥N2b disease associated with the recurrent lesion • Nominal ≥T3 • Poorly differentiated histology and recurrent lesion ≥20 mm in diameter

†High-risk CSCC with both nodal and non-nodal features was categorized as high-risk nodal disease.
ClinicalTrials.gov identifier: NCT03969004. Accessed August 27, 2025. https://clinicaltrials.gov/study/NCT03969004.

- The primary endpoint was DFS.
- Secondary endpoints included FFLRR, FFDR, overall survival, and safety.
- PROs evaluating HRQoL, including health status, functioning, and symptoms were exploratory endpoints.
- PROs were collected using the European Organisation for Research and Treatment of Cancer QLQ-C30[3] and the EQ-5D-3L, with a primary focus on the VAS.[4]
  - PRO questionnaires were electronically administered at baseline, Day 1 of each treatment cycle, and the end of treatment (30 days after the final dose), followed by every 4 months and every 6 months after Year 3.
  - Overall change from baseline across treatment cycles was analyzed on all scales using MMRM among patients in the full analysis set (defined as all randomized patients).
  - Commonly referenced thresholds of 10-point change on the QLQ-C30 and 7 points on the EQ-5D-3L VAS were considered clinically meaningful.[5,6]
- Proportions of patients with clinically meaningful improvement/deterioration or maintenance of PROs were calculated using the thresholds noted above.
- Median time from randomization to the first clinically meaningful deterioration excluding death was determined through follow-up using Kaplan–Meier analyses based on the thresholds defined above and using all PRO assessments through end of follow-up.
- Additional details regarding PRO analyses are in the **Supplementary Methods**.

RESULTS

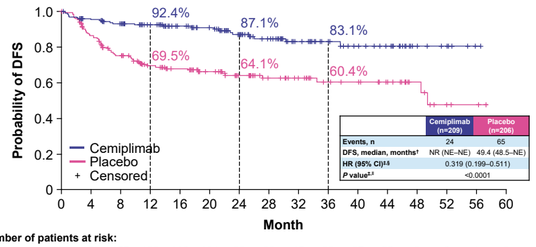
Patient demographics and clinical characteristics

- Overall, patients were predominantly male (83.9%) and White (91.1%), and 70.8% were ≥65 years old (**Supplementary Table 1**).
  - The head and neck region was the most common tumor location (82.7%), and nodal disease (58.3%) was the most common high-risk category (**Supplementary Table 1**).
- Median follow-up from randomization to data cutoff was 24.0 months (range 2–64 months).

Clinical activity

- The Kaplan–Meier estimated DFS curves separated early and remained separated for the duration of follow-up (**Figure 2**).
- Median DFS was not reached in the cemiplimab arm and was 49.4 months in the placebo arm (**Figure 2**).

Figure 2. Kaplan–Meier estimated DFS by treatment



†Based on the Kaplan–Meier method. ‡Stratified by anatomic region of resected high-risk tumor and geographical region. §Based on stratified proportional hazards model. ‖Two-sided *P* value. Significance threshold set to 0.00455 using the O'Brien Fleming alpha spending function.

- In prespecified subgroup analyses, the HRs indicate improved DFS with cemiplimab versus placebo across all analyzed subgroups (**Supplementary Figure 2**).
- Cemiplimab improved FFLRR (HR: 0.20) and FFDR (HR: 0.35) as compared with placebo (**Supplementary Figure 3**).
- At the April 7, 2025, data cutoff (33 deaths), cemiplimab HR for overall survival was 0.78 (95% CI: 0.39–1.56) versus placebo.

Safety

- The median duration of exposure for both treatment arms was about 48 weeks.
- The overall incidence of TEAEs of any grade was comparable in the cemiplimab and placebo arms (**Table 1**).

Table 1. Safety summary

	Cemiplimab (n=205)		Placebo (n=204)	
Duration of exposure, median (range), weeks	47.9 (3–52)		47.7 (3–51)	
TEAEs, regardless of attribution, n (%)	**Any grade**	**Grade ≥3**	**Any grade**	**Grade ≥3**
Any	187 (91)	49 (24)	182 (89)	29 (14)
Serious	36 (18)	31 (15)	19 (9)	14 (7)
Led to treatment discontinuation	20 (10)	16 (8)	3 (1)	2 (1)
Led to death	2 (1)	2 (1)	2 (1)	2 (1)
Treatment-related TEAEs, n (%)	**Any grade**	**Grade ≥3**	**Any grade**	**Grade ≥3**
Any	128 (62)	20 (10)	94 (46)	1 (<1)
Immune-mediated AEs, n (%)	**Any grade**	**Grade ≥3**	**Any grade**	**Grade ≥3**
Any	47 (23)	15 (7)	13 (6)	0

- In the cemiplimab arm there was 1 death due to pneumonia (considered unrelated to treatment) and 1 death due to myositis (considered related to treatment by the investigator).
- In the placebo arm, there was 1 death due to pneumonia and 1 death due to new primary malignant lung neoplasm; both were considered unrelated to treatment.
- The most common TEAEs with cemiplimab were fatigue (22%), pruritus (16%), rash (16%), and diarrhea (16%).

PROs

- PRO completion rates through all treatment cycles were >88% for the QLQ-C30 and ≥81% for the EQ-5D-3L VAS in both arms.
- Baseline scores on all QLQ-C30 scales were similar between treatment arms and showed moderate-to-high GHS/QoL and functioning, and low symptom burden (**Supplementary Table 2**).
- Overall LS mean changes from baseline across treatment cycles were small and similar between treatment arms on all scales (**Table 2**).
- Most patients in both treatment arms reported improvement or stability at Cycle 2 on all QLQ-C30 scales (**Supplementary Figure 4A**) with proportions that were generally maintained to the end of treatment (**Supplementary Figure 4B**), with similar results on the EQ-5D-3L VAS (**Supplementary Figure 5**).

Table 2. MMRM analysis of overall LS mean change from baseline across treatment cycles†

Scale	Overall LS mean change from baseline (95% CI)		Difference in LS means (95% CI)	Nominal *P* value
	Cemiplimab	Placebo		
EORTC QLQ-C30	n=164	n=163		
GHS/QoL	−2.0 (−4.3, 0.4)	−1.0 (−3.4, 1.4)	−0.9 (−3.7, 1.8)	0.496
Functioning scales				
Physical	−1.4 (−3.2, 0.5)	−1.9 (−3.9, 0.0)	0.5 (−1.7, 2.7)	0.630
Role	−4.2 (−7.3, −1.2)	−1.6 (−4.8, 1.5)	−2.6 (−6.2, 0.9)	0.148
Emotional	0.2 (−2.2, 2.7)	−0.4 (−2.9, 2.1)	0.7 (−2.2, 3.5)	0.642
Cognitive	−0.8 (−3.1, 1.5)	−0.8 (−3.1, 1.6)	−0.1 (−2.7, 2.6)	0.973
Social	0.4 (−2.4, 3.2)	0.9 (−1.9, 3.8)	−0.5 (−3.8, 2.7)	0.743
Symptom scales				
Fatigue	5.0 (2.2, 7.7)	4.2 (1.4, 7.0)	0.8 (−2.4, 4.0)	0.639
Nausea/vomiting	1.2 (−0.2, 2.5)	1.4 (−0.1, 2.8)	−0.2 (−1.8, 1.4)	0.826
Pain	3.2 (−0.1, 6.5)	2.1 (−1.3, 5.6)	1.1 (−2.8, 5.0)	0.575
Dyspnea	1.8 (−1.0, 4.6)	2.0 (−0.9, 4.9)	−0.2 (−3.5, 3.0)	0.897
Insomnia	1.9 (−1.7, 5.5)	1.2 (−2.5, 5.0)	0.6 (−3.6, 4.8)	0.769
Appetite loss	−0.9 (−4.0, 2.3)	−2.0 (−5.3, 1.2)	1.1 (−2.5, 4.8)	0.542
Constipation	−1.6 (−4.1, 1.0)	−0.6 (−3.2, 2.1)	−1.0 (−4.0, 2.0)	0.516
Diarrhea	2.9 (0.7, 5.0)	2.8 (0.5, 5.0)	0.1 (−2.4, 2.6)	0.935
EQ-5D-3L	n=155	n=155		
VAS	0.2 (−1.9, 2.2)	0.6 (−1.5, 2.7)	−0.5 (−2.9, 1.9)	0.710

†Better outcomes are indicated by higher scores on the GHS/QoL, functioning scales, and EQ-5D-3L VAS, and lower scores on the symptom scales.

- To provide longer-term estimates of the impact on PROs during follow-up, a post hoc MMRM analysis was conducted that considered time as a continuous variable given that follow-up assessments were not at fixed intervals, and these post hoc results were consistent with the main MMRM analysis; the small changes from baseline were similar between treatment arms (**Data Not Shown**).
- Median time to first clinically meaningful deterioration was similar between treatment arms in all scales (**Supplementary Table 3**).

LIMITATIONS

- The PRO endpoints, being exploratory, were not powered to detect differences between treatment arms; PROs are also not specific for patients with high-risk CSCC and thus may not capture all components of HRQoL; of note, no disease-specific measure has been developed and validated for this population.
- The MMRM analyses assume missing data are missing-at-random, which may not always hold in an oncology trial setting.

CONCLUSIONS

- Cemiplimab is the only systemic therapy to demonstrate a statistically significant and clinically meaningful reduction in disease recurrence as adjuvant therapy for patients at high risk of CSCC recurrence.
- Cemiplimab also improved freedom from both locoregional and distant recurrence, with 80% and 65% reductions versus placebo, respectively.
- The safety profile of cemiplimab for high-risk CSCC in the adjuvant setting is consistent with its profile in the advanced/metastatic CSCC setting and overall cemiplimab profile.
- The moderate-to-high levels of HRQoL and low symptom burden observed at baseline were maintained during adjuvant treatment with cemiplimab, with no clinically meaningful differences versus placebo, suggesting that cemiplimab does not increase the patient burden.
- Adjuvant cemiplimab represents a potential new standard of care for patients at high risk of CSCC recurrence.

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ABBREVIATIONS

AE, adverse event; CSCC, cutaneous squamous cell carcinoma; DFS, disease-free survival; ECE, extracapsular extension; EQ-5D-3L, EuroQol 5-dimension, 3-level questionnaire; FFDR, freedom from distant recurrence; FFLRR, freedom from local-regional recurrence; GHS, global health status; HRQoL, health-related quality of life; LS, least-squares; MMRM, mixed-effects model for repeated measures; NE, not evaluable; NR, not reached; PRO, patient-reported outcome; Q3W, every 3 weeks; Q6W, every 6 weeks; QoL, quality of life; QLQ-C30, Quality of Life Questionnaire Core 30; T3, tumor stage 3; T4, tumor stage 4; TEAE, treatment-emergent adverse event; VAS, visual analog scale.

References, author disclosures, and acknowledgements are available in the **Supplementary Information**.

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