C-POST protocol update: A Phase 3, randomized, double-blind study of adjuvant cemiplimab versus placebo post surgery and radiation therapy in patients with high-risk cutaneous squamous cell carcinoma

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Background

Cutaneous squamous cell carcinoma (CSCC)

- Surgical resection is a standard treatment option for the management of CSCC with a cure rate of >95%. Some patients, however, have high risk of recurrence as assessed by immune status, primary disease stage, extent of nodal involvement, presence of extracapsular extension, and prior treatment.[1,2]
- Postoperative radiation therapy is recommended for patients with high-risk features, but relapse with locoregional recurrence or distant metastases may still occur.[3]

Cemiplimab

- Cemiplimab is an anti–programmed cell death-1 (PD-1) antibody approved in the US and Europe for the treatment of patients with locally advanced or metastatic CSCC who are not candidates for curative surgery or radiotherapy and is approved or under review by other health authorities.[4–8]
- Results from the Phase 1 (NCT02383212) and Phase 2 (NCT02760498) trials of cemiplimab generally demonstrated clinically meaningful activity and an acceptable safety profile in patients with advanced CSCC consistent with other anti–PD-1 agents.[9,10]
- The C-POST study evaluates the efficacy of cemiplimab as adjuvant therapy for patients with high-risk CSCC following surgery and postoperative radiation. Here, we present the most recent study protocol amendment.

Methods

Study design

- C-POST is a randomized, placebo-controlled, double-blind, multicenter Phase 3 study comparing cemiplimab versus placebo as adjuvant therapy for patients with high-risk CSCC after surgery and postoperative radiation (NCT03969004). The revised study design is shown in **Figure 1**.

Treatment

- The study consists of two parts:
- **Part 1:** Randomized (1:1), double-blind, placebo-controlled.
- **Part 2:** Optional open-label cemiplimab treatment (for patients who experience disease recurrence).

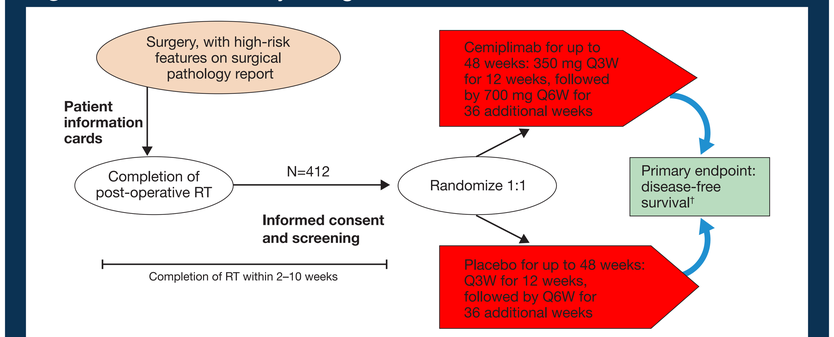
Outcome measures

- **Primary endpoint:** Disease-free survival.
- **Secondary endpoints:** Overall survival, freedom from locoregional and distant recurrence, cumulative occurrence of secondary primary tumors, and safety.
- **Exploratory endpoints:** Pattern of failures, geographic variations in administration of postoperative radiation, health-related quality of life, molecular characterization of pretreatment tumor samples, and circulating tumor DNA detection.

References

1. Breuninger H et al. *J Dtsch Dermatol Ges*. 2013;11 Suppl 3:37–45, 39–47.
2. Stratigos AJ et al. *Eur J Cancer*. 2015;51:1989–2007.
3. Porceddu SV et al. *J Clin Oncol*. 2018;36:1275–1283.
4. Regeneron Pharmaceuticals, Inc. LIBTAYO® (cemiplimab-rwlc) injection, for intravenous use [US prescribing information]; 2021. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/761097s007lbl.pdf. Accessed January 28, 2022.
5. Health Canada. LIBTAYO® – Notice of compliance with conditions – qualifying notice; 2019. Available at: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/notice-compliance/conditions/libtayo-notice-compliance-conditions-218718.html. Accessed January 28, 2022.
6. Brazilian Health Authority – ANVISA. Libtayo (Cemipimab): new indication; 2021. Available at: https://www.gov.br/anvisa/pt-br/assuntos/medicamentos/novos-medicamentos-e-indicacoes/libtayo-cemiplimabe-nova-indicacao. Accessed January 28, 2022.
7. Ministry of Health Israel. The Israeli Drug Registry – LIBTAYO; 2019. Available at: https://israeldrugs.health.gov.il/#!/medDetails/164%2099%2036023%2000. Accessed January 28, 2022.
8. Regeneron Pharmaceuticals, Inc. Libtayo® (cemiplimab) approved by the European Commission as the first immunotherapy indicated for patients with advanced basal cell carcinoma; 2021. Available at: https://www.prnewswire.com/news-releases/libtayo-cemiplimab-approved-by-the-european-commission-as-the-first-immunotherapy-indicated-for-patients-with-advanced-basal-cell-carcinoma-301319988.html. Accessed January 28, 2022.
9. Migden MR et al. *N Engl J Med*. 2018;379:341–351.
10. Migden MR et al. *Lancet Oncol*. 2020;21:294–305.

Figure 1. C-POST study design



†Cemiplimab after disease recurrence permitted if protocol-specified criteria are met.
Q3W, every 3 weeks; Q6W, every 6 weeks; RT, radiation therapy.

Figure 2. High-risk CSCC features

High-risk CSCC features

Nodal disease with ECE and ≥1 node ≥20 mm and/or ≥3 lymph nodes regardless of ECE†	In-transit metastases	T4 lesion	Perineural invasion	Recurrent CSCC
Inclusion 3a	Inclusion 3b	Inclusion 3c	Inclusion 3d	Inclusion 3e
• Per surgical pathology report	• Skin or subcutaneous metastases that are >2 cm from the primary lesion but are not beyond the regional nodal basin	• Including HN and non-HN lesions	• Clinical and/or radiologic involvement of named nerves	• CSCC that arises within the area of the previously resected tumor, plus ≥1 additional feature*

*Additional features:
- ≥N2b disease associated with the recurrent lesion
- Nominal ≥T3 (recurrent lesion ≥4 cm in diameter or minor bone erosion or deep invasion >6 mm measured from the granular layer of normal adjacent epithelium)
- Poorly differentiated histology and ≥20 mm diameter of recurrent lesion. The recurrent lesion must be documented to be within the area of the previously resected CSCC by radial measurement of the greatest radius of the final defect, measured from the estimated center of the original surgical wound

†Defined as extension through the lymph node capsule into the surrounding connective tissue with or without associated stromal reaction.
CSCC, cutaneous squamous cell carcinoma; ECE, extracapsular extension; HN, head and neck.

Summary

- Patients with high-risk CSCC often experience relapse with locoregional recurrence or distant metastases. There is an unmet need to reduce the risk of CSCC recurrence in these patients after curative surgery or radiation.
- The C-POST study is evaluating the efficacy of cemiplimab as adjuvant therapy for patients with high-risk CSCC after surgery and postoperative radiotherapy.
- This study is once again open for enrollment following interruptions owing to the COVID-19 pandemic.

Patient eligibility

Table 1. Key inclusion criteria

- ≥18 years old (in Japan only: ≥21 years old)
- Resection of pathologically confirmed CSCC, with macroscopic gross resection of all diseased area
- High-risk CSCC, defined by at least one of the categories presented in **Figure 2**
- Completion of postoperative radiation therapy (≥50 Gy) within 2–10 weeks of randomization
- ECOG performance status of 0 or 1
- Adequate hepatic, renal, and bone marrow function

CSCC, cutaneous squamous cell carcinoma; ECE, extracapsular extension; ECOG, Eastern Cooperative Oncology Group.

Table 2. Key exclusion criteria

- Squamous cell carcinoma arising from non-cutaneous sites (note: patients with parotid SCC are not excluded if impression of the investigator is that it arose from primary cutaneous lesion)
- Concurrent malignancy other than localized CSCC or history of malignancy other than localized CSCC within 3 years of date of randomization, except for tumors with negligible risk of metastasis or death
- Hematologic malignancies except for patients with CLL who have not required treatment within ≥6 months
- History of solid organ transplant except corneal transplants

CLL, chronic lymphocytic leukemia; CSCC, cutaneous squamous cell carcinoma; SCC, squamous cell carcinoma.

Radiation therapy treatment plan analysis

- Post-operative radiation therapy (RT) is delivered following complete macroscopic resection of high-risk CSCC of head and neck (HN) and non-HN sites, prior to enrollment and randomization into the study. Some patients will enter the study after having received RT at sites that are not participating centers.
- A minimum set of RT details will be collected on all patients in the case report forms. Additionally, retrospective random RT treatment plan review will be performed on approximately 20% of study patients, including the first enrolled in each site whenever possible. This review will be performed by the Trans Tasman Radiation Oncology Group (TROG) Radiation Therapy Treatment Plan Review Committee (RTTPRC).
- A checklist of the source data required for each selected case will be provided by the RTTPRC. This checklist can also be accessed via the TROG website (www.trog.com.au).
- Intensity-modulated radiotherapy is preferable, particularly for HN sites, but all forms of RT including three-dimensional conformal radiotherapy and electron beam therapy are acceptable.

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