A Phase 3, Randomized, Double-Blind Study of Adjuvant Cemiplimab Versus Placebo Post-Surgery and Radiation in Patients with High-Risk Cutaneous Squamous Cell Carcinoma (CSCC)

Danny Rischin,[1] Matthew G. Fury,[2] Israel Lowy,[2] Elizabeth Stankevich,[3] Siyu Li,[2] Hyunsil Han,[2] Sandro V. Porceddu[4]

[1]Department of Medical Oncology, Peter MacCallum Cancer Centre, Melbourne, Australia; [2]Regeneron Pharmaceuticals, Inc., Tarrytown, NY, USA; [3]Regeneron Pharmaceuticals, Inc., Basking Ridge, NJ, USA; [4]School of Medicine, University of Queensland, Herston, Queensland, Australia; Department of Radiation Oncology, Princess Alexandra Hospital, Woolloongabba, Queensland, Australia.

Background

Cutaneous squamous cell carcinoma (CSCC)

- CSCC is the second most common skin cancer with an estimated incidence of around 1 million cases per year in the US.[1] Worldwide, reports show an annual rise in incidence of 3–7% in most countries.[2]
- While the surgical cure rate for CSCC is approximately 95%, a proportion of patients are considered to be at high risk for recurrence as assessed by immune status, primary disease stage, extent of nodal involvement, presence of extracapsular extension, and prior treatment.[3,4]
- Post-operative radiation is recommended for some patients with CSCC after surgery, but locoregional or distant recurrence can still occur.
- POST, the largest prospective randomized adjuvant CSCC study, provided new insights into risk factors for CSCC recurrence.[5]

Cemiplimab

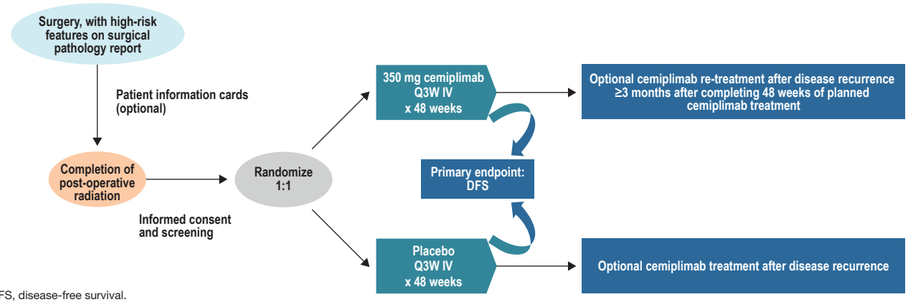
- Cemiplimab is a high-affinity, highly potent human monoclonal antibody directed against the programmed cell death (PD)-1 receptor.[6,7]
- In Phase 1 and Phase 2 trials (NCT02383212 and NCT02760498, respectively), cemiplimab exhibited antitumor activity with a safety profile comparable to those of other anti–PD-1 inhibitors in patients with advanced malignancies, including CSCC.[7–9]
  - For the latest data from the Phase 2 study of cemiplimab in patients with advanced CSCC, please see poster 367 reporting longer follow-up data and poster 382 reporting post hoc analysis of health-related quality of life.
- Cemiplimab (cemiplimab-rwlc in the US) is the only therapy approved by the US Food and Drug Administration and the European Commission for treatment of patients with metastatic or locally advanced CSCC who are not candidates for curative surgery or curative radiation.[10,11]
- While the clinical activity of cemiplimab as monotherapy has been established in patients with advanced CSCC who are not candidates for curative surgery or curative radiation, this study aims to evaluate its benefit as an adjuvant treatment following surgery and post-operative radiation in patients with CSCC at high risk for recurrence.

Methods

Study design

- This randomized, placebo-controlled, double-blind, multicenter Phase 3 trial (C-POST) is evaluating the clinical activity of adjuvant cemiplimab versus placebo in patients with high-risk CSCC, after surgery and post-operative radiation (NCT03969004).
- The study consists of two parts:
  - Part 1: Double blind, randomized, placebo-controlled
    - Study treatment: 30-minute infusions of cemiplimab 350 mg or placebo intravenously (IV) every 3 weeks (Q3W) for up to 48 weeks or until unacceptable toxicity, disease recurrence, death, or withdrawal of consent
    - Duration: A screening period of up to 28 days prior to randomization, a treatment period of up to 48 weeks, and a follow-up period of up to disease recurrence or end of study (**Figure 1**).
  - Part 2: Optional open-label
    - Treatment: Cemiplimab IV 350 mg Q3W
    - Duration of treatment: Up to 96 weeks in Part 2 or until disease progression, unacceptable toxicity, withdrawal of consent, death, or loss to follow-up.

Figure 1. C-POST study design



DFS, disease-free survival.

Outcome measures

- The primary objective of the study is to compare DFS of patients with high-risk CSCC treated with adjuvant cemiplimab versus placebo after surgery and post-operative radiation.
- The secondary objectives of the study are to compare the following measures with cemiplimab versus placebo after surgery and post-operative radiation in the aforementioned patient population:
  - Overall survival (OS)
  - Freedom from locoregional recurrence
  - Freedom from distant recurrence
  - Cumulative incidence of second primary CSCC tumors
  - Safety.
- The exploratory objectives of the study are:
  - To evaluate patterns of failure in patients treated with cemiplimab or placebo
  - To explore geographic/regional variations in administration of post-operative radiation in patients treated with cemiplimab or placebo
  - To compare health-related quality of life in patients treated with cemiplimab versus placebo
  - To explore associations between clinical activity of cemiplimab and molecular features in pre-treatment tumor samples.

Patient eligibility

- Adult patients with high-risk CSCC who have undergone surgical resection followed by radiation are eligible for study enrollment (**Tables 1 and 2**).

Table 1. Key inclusion criteria

- ≥18 years old (in Japan only: ≥21 years old)
- Resection of pathologically confirmed CSCC (primary CSCC lesion only, or primary CSCC with nodal involvement, or CSCC nodal metastasis with known primary CSCC lesion previously treated within the draining lymph node echelon) with macroscopic gross resection of all diseased area
- High-risk CSCC, defined by at least one of the following:
  - Nodal disease with extracapsular extension, defined as extension through the lymph node capsule into the surrounding connective tissue with or without associated stromal reaction, and at least one node of >20 mm on the surgical pathology report[3]
  - In-transit metastases, defined as skin or subcutaneous metastases of >2 cm from the primary lesion but are not beyond the regional nodal basin[12]
  - T4 lesion, including head and neck lesions and non-head-and-neck lesions[3,13]
  - Perineural invasion, defined as clinical and/or radiologic involvement of named nerves[13]
  - Recurrent CSCC, defined as CSCC that arises within the area of the previously resected tumor, plus at least one of the following additional features[3]:
    - ≥N2b disease associated with the recurrent lesion
    - Nominal ≥T3 (recurrent lesion of ≥4 cm in diameter, minor bone erosion, or deep invasion of >6 mm measured from the granular layer of normal adjacent epithelium)
    - Poorly differentiated histology and recurrent lesion of ≥20 mm diameter
- Completion of curative-intent post-operative radiation within 2 to 6 weeks of randomization
- Eastern Cooperative Oncology Group performance status of 0 or 1
- Adequate hepatic, renal and bone marrow functions

Table 2. Key exclusion criteria

- Squamous cell carcinoma arising from non-cutaneous sites
- Concurrent malignancy other than localized CSCC and/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
- History of distantly metastatic CSCC (visceral or distant nodal), unless disease-free interval is ≥3 years
- Ongoing or recent (within 5 years) autoimmune disease that requires treatment
- Participation in a study of an investigational agent or an investigational device within 4 weeks of the randomization date or five half-lives
- Prior systemic anti-cancer immunotherapy for CSCC
- Receipt of immunosuppressive corticosteroid (>10 mg prednisone daily or equivalent) within 4 weeks prior to the first dose of cemiplimab or placebo
- Anticancer systemic therapy within 4 weeks or lack of recovery from any acute toxicities
- Prior allogeneic stem cell transplantation, or autologous stem cell transplantation
- Any infection requiring hospitalization and/or intravenous antibiotic therapy within 2 weeks of the randomization date
- Uncontrolled infection with human immunodeficiency virus, hepatitis B or hepatitis C virus; or diagnosis of immunodeficiency
- History of immune-related pneumonitis within 5 years
- History of documented allergic reactions or acute hypersensitivity reaction attributed to any antibody treatment
- History of solid organ transplant except corneal transplant(s)
- Breastfeeding women
- Women of childbearing potential or sexually active men who are unwilling to practice highly effective contraception

Statistical assumptions and analysis

- The primary clinical hypothesis of the study is that cemiplimab prolongs DFS as compared with placebo.
- The primary analysis of DFS will be performed with a 2-sided alpha at 0.05 overall significance level for the following null and alternative statistical hypotheses:
  - H_0: The survival curve of DFS for cemiplimab is the same as that for placebo
  - H_1: The survival curve of DFS for cemiplimab is not the same as that for placebo.
- The full analysis set will include all randomized patients (intent-to-treat population) and will be used for analyses of efficacy endpoints.
- The safety analysis set will include all randomized patients who received any study drug (as-treated population) and will be used for analyses of all safety variables.
- The primary endpoint of DFS will be tested by stratified log-rank test at 2-sided 0.05 significance level.

Summary

- Patients with high-risk CSCC often experience relapse with locoregional recurrence or distant metastases despite initial treatment with surgery and post-operative radiation.
- Cemiplimab, a PD-1 monoclonal antibody, has demonstrated clinical activity with a safety profile comparable to those of other anti–PD-1 agents in advanced malignancies, including CSCC.
  - Cemiplimab (cemiplimab-rwlc in the US) is the only therapy approved by the US Food and Drug Administration and the European Commission for treatment of patients with metastatic or locally advanced CSCC who are not candidates for curative surgery or curative radiation.
- This study will provide insight into the clinical activity of cemiplimab versus placebo as an adjuvant treatment in patients with CSCC at high risk for recurrence, after surgery and post-operative radiation.
- This study is ongoing and is actively enrolling patients.

References

1. Potenza C et al. *Biomed Res Int*. 2018:9489163–9489163.
2. Radiation WSU. *Global burden of disease from solar ultraviolet radiation*. Environmental Burden of Disease Series, no. 13. World Health Organization, Geneva. 2006.
3. Breuninger H et al. *J Dtsch Dermatol Ges*. 2013;11(Suppl 3):37–45, 39–47.
4. AJCC. *Cancer Staging Manual*. 8th ed: American College of Surgeons & Springer International Publishing; 2017.
5. Porceddu S et al. *J Clin Oncol*. 2018;36:1275–1283
6. Burova E et al. *Mol Cancer Ther*. 2017;16:861–870.
7. Migden MR et al. *N Engl J Med*. 2018;379:341–351.
8. Migden MR et al. *Lancet Oncol*. 2020;21:294–305.
9. Papadopoulos KP et al. *Clin Cancer Res*. 2020;26:1025–1033.
10. Regeneron Pharmaceuticals, Inc. LIBTAYO® (cemiplimab-rwlc) injection full US prescribing information. Available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/761097s000lbl.pdf, accessed March 30, 2020.
11. European Medicines Agency. LIBTAYO® EPAR. Available at https://www.ema.europa.eu/en/medicines/human/EPAR/libtayo, accessed March 30, 2020.
12. Leitenberger JJ et al. *J Am Acad Dermatol*. 2016;75:1022–1031.
13. UICC. *Manual of Clinical Oncology*. 9th ed. Union for International Cancer Control (UICC) and John Wiley & Sons, Ltd; 2015.

Acknowledgments

The authors would like to thank the patients, their families, all other investigators and all investigational site members involved in this study.

The study was funded by Regeneron Pharmaceuticals, Inc., and Sanofi. Medical writing support and typesetting was provided by Bu Reinen, PhD, of Prime, Knutsford, UK, funded by Regeneron Pharmaceuticals, Inc. and Sanofi.

For any questions or comments, please contact Dr Danny Rischin, Danny.Rischin@petermac.org.

Poster presented at the American Society of Clinical Oncology (ASCO) 2020 Virtual Scientific Meeting, May 29–31, 2020 (encore of 2019 European Society for Medical Oncology Annual Meeting poster).