Name: Michael L. Andria, Pharm.D.
Organization: Regeneron Pharmaceuticals, Inc.
Address: 777 Old Saw Mill River Road, Tarrytown, NY 10591
Phone: (304) 777-9579
E-mail: michael.andria@regeneron.com
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NCCN Guidelines Panel: Non-Melanoma Skin Cancer

Dear NCCN Guidelines Non-Melanoma Skin Cancer Panel:

On behalf of Regeneron Pharmaceuticals, Inc. and of Sanofi Genzyme, we respectfully request the Non-Melanoma Skin Cancer Panel to review the enclosed data for inclusion of cemiplimab as the preferred systemic treatment option for the management of patients with advanced cutaneous squamous cell carcinoma (CSCC).

Specific changes requested:

Within the NCCN Squamous Cell Skin Cancer Guidelines (Version 2.2018):

- While maintaining the importance of multidisciplinary tumor board consultation, identify cemiplimab as the preferred intervention (per the NCCN Categories of Preference) among systemic treatment options, for eligible adult patients with advanced cutaneous squamous cell carcinoma, which includes metastatic CSCC (mCSCC) [nodal or distant] or locally advanced CSCC (laCSCC).
- Revision of statements referring to systemic treatment options within the NCCN Guidelines for Head and Neck Cancers where data support the use of cemiplimab in advanced CSCC.

FDA clearance:

Cemiplimab is an investigational compound under development by Regeneron Pharmaceuticals, Inc. and Sanofi Genzyme. The FDA has granted breakthrough designation for cemiplimab for patients with advanced CSCC. On April 30, 2018, the FDA granted priority review to the BLA of cemiplimab for the treatment of patients with metastatic CSCC or patients with locally advanced CSCC who are not candidates for surgery. The PDUFA date for FDA decision is October 28, 2018; however, the decision may occur sooner.[1,2]

Rationale:

For patients with advanced CSCC, there are currently neither approved systemic treatment options for patients with advanced CSCC nor any public information that other agents are under review with the FDA for the same indication. Data on other systemic therapies in advanced CSCC, such as cytotoxic chemotherapy and targeted therapy, are sparse and show limited activity, limited duration of response, and considerable toxicity.[3]

Safety and efficacy of cemiplimab has been evaluated in 2 prospective clinical trials in patients with mCSCC (nodal and/or distant) or laCSCC who were not candidates for surgery, which together comprise the single largest prospective data set evaluating systemic therapy in this population.[4]

- Study 1: A single-arm, open-label, phase 1 study in patients with a variety of advanced solid tumors, including 16 patients with mCSCC and 10 patients with laCSCC.[4] These 2 expansion cohorts were implemented after an index case of a patient with mCSCC who experienced a complete response in the original dose escalation stages of the study.[5]
- Study 2: A single-arm, open-label, phase 2 study in patients with mCSCC (Group 1 and Group 3) and laCSCC (Group 2). Each group is statistically independent, so results can be analyzed separately. This study is still ongoing.[4]

Patients in both studies received cemiplimab as an intravenous infusion over 30 minutes until confirmed disease progression, unacceptable toxicity, or completion of protocol treatment. Cemiplimab was dosed at 3 mg/kg every 2 weeks in Study 1 and Study 2, Groups 1 and 2, and 350mg every 3 weeks in Study 2 Group 3.[4]

The primary endpoint was confirmed overall response rate (ORR), as assessed by independent central review. For patients with mCSCC without externally visible target lesions, ORR was determined by RECIST 1.1. For laCSCC and mCSCC patients with externally visible target lesions, ORR was determined by a composite endpoint that integrated ICR assessments of radiologic data (RECIST 1.1) and digital medical photography (WHO criteria). Key secondary endpoints included duration of response, progression-free survival (PFS), overall survival (OS), complete response rate, and QOL by EORTC QLQ-C30.[4]

Efficacy and safety results for the 26 patients (16 mSCCC and 10 laCSCC) from Study 1 and 59 mCSCC patients from Group 1 of Study 2, who were evaluable for efficacy at the time of data cut-off, are summarized below.[4]

The median duration of follow-up for Study 1 is 11.0 months (range, 1.1 to 17.0) and for Study 2 is 7.9 months (range, 1.1 to 15.6). In both studies, the median PFS, median OS, and median duration of response had not been reached at the time of data cut-off.[4]

Efficacy Endpoints	**laCSCC (n=10)***	**mCSCC (n=75)**
Confirmed Overall Response Rate		
ORR (95% CI), % (95% CI)	60.0 (26.2 – 87.8)	46.7 (35.1 – 58.6)
Complete Response, no. (%)	0	4 (5.3)
Not evaluable‡, no. (%)	2 (20.0)	8 (10.7)
Time to response		
Median (range), months	3.7 (1.8 – 7.3)	1.9 (1.7 – 6.0)
Durable Disease Control¶, % (95% CI)	70.0 (34.8 – 93.3)	61.3 (49.4 – 72.4)

CI = confidence interval
Data cut-off date: October 2017.
*Patients with locally advanced CSCC according to the Phase 2 definition (i.e. no nodal or distant metastasis) from the Phase 1 CSCC expansion cohorts
‡Patients with non-measurable disease on central review of baseline imaging
¶Defined as the proportion of patients without progressive disease for at least 105 days

The duration of response, in patients who had a response, exceeded 6 months in 7/13 (54%) in laCSCC and mCSCC patients in Study 1 and 16/28 (57%) in mCSCC patients in Study 2.[4]

The most common adverse events of any grade in advanced CSCC patients from Study 1 and Study 2 were fatigue, constipation, decreased appetite, diarrhea, hypercalcemia, hypophosphatemia, nausea, urinary tract infection, and rash. The only investigator-assessed treatment-related adverse events Grade ≥3 that occurred in more than 1 patient was pneumonitis (n=3). The safety profile of cemiplimab appears to be similar to other therapies in this class. [4,6]

The following resources are submitted to assist the committee in their review:

- Migden MR, Rischin D, et al. PD-1 Blockade with Cemiplimab in Advanced Cutaneous Squamous Cell Carcinoma. N Engl J Med. 2018 Jun 4. doi: 10.1056/NEJMoa1805131.
- Migden MR, Rischin D, et al. PD-1 Blockade with Cemiplimab in Advanced Cutaneous Squamous Cell Carcinoma. N Engl J Med. 2018; Suppl: S1-S10. doi: 10.1056/NEJMoa1805131.
- Owonikoko TK, et al. (2018, June). Phase 1 study of cemiplimab, a human monoclonal anti-PD-1, in patients with unresectable locally advanced or metastatic cutaneous squamous cell carcinoma (CSCC): Final efficacy and safety data. Poster session presented at the American Society of Clinical Oncology, Chicago, IL.
- Rischin D, et al. (2018, June). Primary analysis of phase 2 results for cemiplimab, a human monoclonal anti-PD-1, in patients with metastatic cutaneous squamous cell carcinoma (mCSCC) Poster session presented at the American Society of Clinical Oncology, Chicago, IL
- Papadopoulos KP, et al. (2016, June). A first-in-human of REGN2810, a fully human monoclonal antibody against programmed death-1 (PD-1), in combination with immunomodulators including hypofractionated radiotherapy (hfRT). Poster session presented at the American Society of Clinical Oncology, Chicago, IL.

We appreciate the opportunity to provide this information for review by the NCCN Guidelines Non-Melanoma Skin Cancer Panel. Once approved, the product labeling information will promptly be submitted as a supplement to this original submission. Thank you for your time and consideration of this request.

Sincerely,

Michael L. Andria, Pharm.D.

Clinical References:

1. Regeneron Pharmaceuticals, Inc. (2017, Sept). Regeneron and Sanofi Announce Cemiplimab (REGN2810) Has Received FDA Breakthrough Therapy Designation for Advanced Cutaneous Squamous Cell Carcinoma [Press release]. Retrieved from http://investor.regeneron.com/releasedetail.cfm?ReleaseID=1039633
2. Regeneron Pharmaceuticals, Inc. (2018, April). FDA To Conduct Priority Review Of Cemiplimab as a Potential Treatment for Advanced Cutaneous Squamous Cell Carcinoma [Press release]. Retrieved from http://investor.regeneron.com/releasedetail.cfm?releaseid=1065392
3. Cranmer LD, et al. Treatment of Unresectable and Metastatic Cutaneous Squamous Cell Carcinoma. The Oncologist. 2010;15:1320–1328.
4. Migden MR, Rischin D, et al. PD-1 Blockade with Cemiplimab in Advanced Cutaneous Squamous Cell Carcinoma. N Engl J Med. 2018 Jun 4. doi: 10.1056/NEJMoa1805131.
5. Falchook et al. Responses of metastatic basal cell and cutaneous squamous cell carcinomas to anti-PD1 monoclonal antibody REGN2810. J Immunother Cancer. 2016 Nov 15;4:70. doi: 10.1186/s40425-016-0176-3. eCollection 2016.
6. Migden MR, Rischin D, et al. PD-1 Blockade with Cemiplimab in Advanced Cutaneous Squamous Cell Carcinoma. N Engl J Med. 2018; Suppl: S4-S10. doi: 10.1056/NEJMoa1805131.