Libtayo (Cemiplimab-rwlc), a PD-1 Inhibitor, First Drug Approved by the FDA for Advanced Cutaneous Squamous-Cell Carcinoma

By Loretta Fala, Medical Writer

Cutaneous squamous-cell carcinoma (CSCC) is a type of nonmelanoma skin cancer that affects the squamous cells in the middle and outer layers of the skin. CSCC occurs most frequently on sun-exposed areas, such as the scalp, ears, lips, face, neck, and backs of the hands. Less often, CSCC can be in the skin of the genital area.

Some cases of CSCC start as actinic keratosis, a precancerous condition that is caused by excessive sun exposure. Factors that increase the risk for CSCC include excessive exposure to the sun or other ultraviolet light (ie, tanning beds), fair skin, and a weakened immune system, including people with leukemia or lymphoma, or those using immunosuppressant therapy.

CSCC is the second most common form of skin cancer, accounting for 2 of 10 skin cancers (the most common skin cancer is basal-cell carcinoma). Approximately 700,000 Americans are diagnosed with CSCC annually. The mortality rate for CSCC is not known, because unlike other types of cancer, statistics related to CSCC are not reported to cancer registries.

The treatment of CSCC is generally based on the size, location, stage of the carcinoma, and the patient’s preferences. Treatments for CSCC include simple excision, Mohs surgery, cryotherapy, photodynamic therapy, curettage and electrodesiccation, laser therapy, and radiation therapy.

Many patients can be cured with surgical resection. However, patients with advanced CSCC, including regional node involvement or metastases to distant tissues and organs, may not respond to surgery or radiation. Until recently, the treatment for advanced CSCC was limited to clinical trials or to therapies for other cancers (ie, chemotherapy, immunotherapy, systemic therapy).

Libtayo First Drug Approved for CSCC

On September 28, 2018, the US Food and Drug Administration (FDA) approved cemiplimab-rwlc (Libtayo; Regeneron/Sanofi US) for the treatment of patients with locally advanced or metastatic CSCC who are not candidates for curative surgery or curative radiation. Cemiplimab-rwlc, a programmed-cell death receptor (PD)-1 inhibitor, is the first drug (and the first immune checkpoint inhibitor) to be approved by the FDA for the treatment of patients with advanced CSCC. The FDA granted cemiplimab-rwlc a breakthrough therapy and a priority review designation for this indication.

"With the Libtayo approval, the FDA has approved six immune checkpoint inhibitors targeting the PD-1/PD-L1 pathway for treating a variety of tumors, from bladder to head and neck cancer, and now advanced CSCC. This type of cancer can be difficult to treat effectively when it is advanced, and it is important that we continue to bring new treatment options to patients," said Richard Pazdur, MD, Director, FDA’s Oncology Center of Excellence, on the approval of cemiplimab-rwlc.

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Mechanism of Action

Cemiplimab-rwlc is a recombinant human immunoglobulin G4 monoclonal antibody that targets and blocks the PD-1 pathway, thus helping the immune system to fight cancer cells. Cemiplimab-rwlc binds to the PD-1 receptor found on T-cells, blocking its interaction with PD ligand 1 (PD-L1) and PD-L2, thereby inhibiting T-cell proliferation and cytokine production.

Dosing and Administration

Cemiplimab-rwlc is available as a 350-mg/7-mL (50-mg/mL) injection solution in a single-dose vial for intravenous (IV) administration. The recommended dose of cemiplimab-rwlc is 350 mg, administered as an IV infusion for 30 minutes every 3 weeks until disease progression or unacceptable toxicity.
Efficacy Results with Cemiplimab-rwlc in Patients with Metastatic or Locally Advanced Cutaneous Squamous-Cell Carcinoma

<table>
<thead>
<tr>
<th>Efficacy end points ( ^a )</th>
<th>Metastatic CSCC (N = 75)</th>
<th>Locally advanced CSCC (N = 33)</th>
<th>Metastatic and locally advanced CSCC (N = 108)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective response, %</td>
<td>46.7 (95% CI, 35.1-58.6)</td>
<td>48.5 (95% CI, 30.8-66.5)</td>
<td>47.2 (95% CI, 37.5-57.1)</td>
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<tr>
<td>Complete response, %</td>
<td>5.3</td>
<td>0</td>
<td>3.7</td>
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<tr>
<td>Partial response, %</td>
<td>41.3</td>
<td>48.5</td>
<td>43.5</td>
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<tr>
<td>Duration of response</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range, mo</td>
<td>2.8-15.2d</td>
<td>1-12.9d</td>
<td>1-15.2d</td>
</tr>
<tr>
<td>Patients with response lasting</td>
<td>21 (80)</td>
<td>10 (63)</td>
<td>31 (61)</td>
</tr>
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\( ^a \) Median duration of follow-up for metastatic CSCC, 8.1 months; for locally advanced CSCC, 10.2 months; for combined CSCC, 8.9 months.

\( ^b \) Only patients with complete healing of previous cutaneous involvement are included; patients with locally advanced CSCC in Study 1540 required biopsy to confirm complete response.

\( ^c \) Response was ongoing at last assessment.

\( ^d \) Indicates confidence interval; CSCC, cutaneous squamous-cell carcinoma.

Source: Libtayo (cemiplimab-rwlc) injection prescribing information; October 2018.

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Pivotal Clinical Trials: Study 1423 and Study 1540

The efficacy of cemiplimab-rwlc was established in 2 open-label, nonrandomized, multicohort studies, Study 1423 (N = 26) and Study 1540 (N = 82). Both studies included patients (median age, 71 years) with metastatic (nodal or distant) CSCC or locally advanced CSCC who were not candidates for curative surgery or curative radiation. Both studies excluded patients with an auto-immune disease that required systemic treatment with immunosuppressant drugs within 5 years; a history of solid organ transplantation; previous treatment with anti-PD-1/PD-L1 inhibitors or other immune checkpoint inhibitors; presence of HIV, hepatitis B, or hepatitis C infection; or an Eastern Cooperative Oncology Group performance score ≥2.

Patients received cemiplimab-rwlc 3 mg/kg IV every 2 weeks for up to 48 weeks in Study 1423 and up to 96 weeks in Study 1540. Patients continued to receive treatment until disease progression, unacceptable toxicity, or until completion of planned treatment. Tumor response was monitored every 8 weeks. The key efficacy end points were the confirmed objective response rate, as measured by independent central review, and the independent central review–assessed duration of response.

Of the 75 patients with metastatic CSCC, 46.7% achieved an objective response rate, as measured by independent central review; of the 33 patients with locally advanced CSCC, 48.5% achieved an objective response rate. Furthermore, 60% of patients with metastatic CSCC and 63% of patients with locally advanced CSCC maintained a response to treatment for ≥6 months.

Adverse Reactions

The most common (≥20%) adverse reactions reported with cemiplimab-rwlc therapy were fatigue (29%), rash (25%), and diarrhea (22%). The most common (≥2%) grade 3 to 4 adverse reactions were cellulitis, sepsis, hypertension, pneumonia, musculoskeletal pain, skin infection, urinary tract infection, and fatigue.

Overall, 5% of patients discontinued treatment because of adverse events; adverse reactions leading to treatment discontinuation were pneumonitis, autoimmune myocarditis, hepatitis, aseptic meningitis, complex regional pain syndrome, cough, and muscular weakness.

Cemiplimab-rwlc has no contraindications.

Use in Specific Populations

Data are not available on the use of cemiplimab-rwlc in pregnant women; the drug’s mechanism of action suggests that it can cause fetal harm. Data are not available on the effect of cemiplimab-rwlc on a breastfeeding child or on milk production. Women should not breastfeed during treatment with cemiplimab-rwlc and for at least 4 months after the last dose, because of the potential for serious adverse reactions in breastfed children.

In clinical studies, 72% of patients were aged ≥65 years; no overall differences were observed between these patients and younger patients.

Warnings and Precautions

Immune-mediated responses, some severe or fatal, can occur with cemiplimab-rwlc in any organ system or tissue; these immune-mediated responses include pneumonitis, colitis, hepatitis, endocrinopathies, dermatologic adverse reactions, and nephritis with renal dysfunction. Patients should be monitored for signs and symptoms of any immune-mediated adverse reaction, and liver and thyroid function should be evaluated at baseline and at intervals during treatment. If an immune-mediated reaction occurs, cemiplimab-rwlc should be withheld or permanently discontinued, depending on the severity of the reaction.

Patients should be monitored for infusion-related reactions. If a grade 1 or 2 infusion-related reaction occurs, cemiplimab-rwlc should be interrupted or its rate of infusion should be slowed. If a grade 3 or 4 reaction occurs, the drug should be permanently discontinued.

Embryo-fetal toxicity can occur with cemiplimab-rwlc. Women of reproductive potential should use effective contraception during treatment with cemiplimab-rwlc and for at least 4 months after the last dose.
Conclusion

Designated by the FDA as a breakthrough therapy, cemiplimab-rwlc became the first drug to receive FDA approval for the treatment of patients with advanced CSCC. Cemiplimab-rwlc, a PD-1–blocking antibody, demonstrated an objective response rate in 47.2% of patients with metastatic or with locally advanced CSCC who are not candidates for curative surgery or curative radiation. Furthermore, 61% of patients with metastatic or locally advanced CSCC who received cemiplimab-rwlc maintained a clinical response for ≥6 months.

References