

# Evidence-Based ONCOLOGY

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## Cemiplimab Associated With High Response and Duration of Response in Patients With Locally Advanced Cutaneous Squamous Cell Carcinoma

Lynne Lederman, PhD

**NEW STUDY RESULTS SUGGEST** that cemiplimab is the new standard of care for treating locally advanced cutaneous squamous cell carcinoma (laCSCC). At the 2019 American Society of Clinical Oncology (ASCO) Annual Meeting, Michael R. Migden, MD, of the Department of Dermatology at The University of Texas MD Anderson Cancer Center in Houston, presented a primary analysis of group 2, phase 2 trial results of cemiplimab-rwlc, a human monoclonal anti programmed cell death protein (PD-1) antibody, for the treatment of patients with laCSCC (NCT02760498).<sup>1</sup>

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## Ribociclib Improves Survival by Nearly 30% for Premenopausal Women With Advanced Breast Cancer

Silas Inman

**TREATMENT WITH THE COMBINATION** of ribociclib (Kisqali) and endocrine therapy demonstrated an estimated overall survival (OS) rate of 70.2% at 42 months compared with 46.0% for placebo and endocrine therapy in peri- or premenopausal women with hormone receptor (HR)-positive, HER2-negative advanced breast cancer, according to updated

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## Cemiplimab Associated With High Response and Duration of Response in Patients With Locally Advanced Cutaneous Squamous Cell Carcinoma

(continued from cover)

Advanced CSCC includes metastatic (nodal and/or distant) and laCSCC, which, when not amenable to surgery and/or radiotherapy, have a high mortality rate and a poor prognosis, representing an unmet medical need.<sup>2</sup> Until recently, no approved systemic therapy for patients with advanced CSCC was available. Cemiplimab-rwlc is a high-affinity, human, hinge-stabilized monoclonal antibody to the PD-1 receptor that potently blocks the interactions of PD-1 with PD-ligand 1 (PD-L1) and PD-ligand 2. It is approved in the United States for the treatment of patients with metastatic CSCC or laCSCC who are not candidates for curative surgery or curative radiation.<sup>3</sup>

On June 11, 2019, the FDA approved pembrolizumab, another PD-1 blocking antibody, in combination with platinum and fluorouracil for the first-line treatment of patients with metastatic or unresectable, recurrent head and neck squamous cell carcinoma. It was approved as a single agent for the first-line treatment in patients whose tumors express PD-L1 (combined positive score,  $\geq 1$ ), as determined by an FDA-approved test, and as a single agent for patients with disease progression on or after platinum-containing chemotherapy.<sup>4,5</sup>

Cemiplimab was associated with substantial antitumor activity and durable responses in patients with metastatic and laCSCC in the expansion cohorts in a phase 1 study and in patients with metastatic CSCC (group 1) in a phase 2 study (EMPOWER-CSCC-1; NCT02760498).<sup>6,7</sup>

### Data Analysis

In addition to data from the primary analysis of patients in group 2 of the nonrandomized, pivotal phase 2 study in laCSCC, the investigators presented biomarker data.<sup>1</sup> This primary analysis of group 2, with a data cutoff of October 10, 2018, included 78 adult patients with laCSCC who had lesions that investigators determined were not amenable to surgery or radiotherapy. This study included patients who had CSCC with significant local invasion that precluded complete resection or CSCC that was technically amenable to surgery but clinically inappropriate, such as occurrence in a location in which surgery could result in severe disfigurement or dysfunction, recurrence in the same location after  $\geq 2$  surgical procedures and with curative resection deemed unlikely, or other contraindications for surgery. Radiotherapy could be considered inappropriate for patients who would receive an acceptable cumulative dose due to prior radiotherapy, predicted lack of response to radiotherapy, or other contraindications.

The primary goal of the study was to evaluate the objective response rate (ORR), the complete response (CR) plus partial response (PR), according to independent central review per Response Evaluation Criteria in Solid Tumors 1.1 (for scans) and modified World Health Organization criteria (for photographs). Secondary objectives included

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estimation of ORR by investigator assessments, duration of response (DOR), progression-free survival (PFS), and overall survival (OS). Investigators also assessed safety and tolerability of cemiplimab and durable disease control rate (defined as the proportion of patients without progressive disease for at least 105 days).

Protocol-defined exploratory objectives (biomarker studies) included the association between PD-L1 immunohistochemistry and tumor mutational burden (TMB) and clinical activity of cemiplimab. PD-L1 expression level was assessed by the PD-L1 immunohistochemistry 22C3 assay (Agilent Technologies) in formalin-fixed, paraffin-embedded core needle or punch tumor biopsy samples and quantified as the percentage of tumor cells with detectable PD-L1 membrane staining (tumor proportion score [TPS]). TMB was estimated in the DNA samples extracted from the formalin-fixed, paraffin-embedded tumor biopsies using the analytically validated TruSight Oncology 500 assay (Illumina, Inc).

Patients in group 2 were treated with cemiplimab 3 mg/kg intravenously twice weekly for up to 96 weeks, with retreatment optional for patients with disease progression during follow-up. Tumor imaging was conducted every 8 weeks to assess efficacy. Key exclusion criteria included ongoing or recent (within 5 years) autoimmune disease requiring systemic immunosuppression, prior anti-PD-1 or anti-PD-L1 therapy, and history of solid organ transplantation, hematologic malignancies, or concurrent malignancies (unless indolent or not considered life-threatening; eg, basal cell carcinoma).

The median patient age was 74 years, 75.6% of patients were male, and an Eastern Cooperative Oncology Group performance status of 0 or 1 was almost equally divided between patients. The primary CSCC site was the head/neck (79.5%), an extremity (17.9%), and the trunk (2.6%). Only 15.4% of patients had undergone prior cancer-related systemic therapy, whereas 55.1% had received prior cancer-related radiotherapy.

Reasons for contraindication of surgery included an anatomically challenging location that could result in severe disfigurement or dysfunction (38.5%), recurrent lesion in the same location after  $\geq 2$  surgical procedures with curative resection unlikely (32.1%), and local invasion that precluded complete resection (25.6%). In about half of patients, the risk-benefit assessment contraindicated radiotherapy; tumors were not expected to respond to radiotherapy in 21.8%, and prior radiotherapy precluded further radiotherapy in 12.8%.

At the time of data cutoff, 5 patients had completed the planned treatment, 24 (30.8%) remained on

treatment, and 49 (62.8%) had discontinued treatment mainly because of disease progression ( $n = 17$ ; 21.8%) and adverse events (AEs), investigator's decision, CR to cemiplimab, or patient's decision (6 each, 7.7%).

The median duration of exposure to cemiplimab was 7.9 months with a median of 17 doses administered. The median duration of follow-up at the time of data cutoff was 9.3 months.

By independent central review, the ORR was 43.6% (95% CI, 32.4-55.3), with 10 CRs and 24 PRs. By investigator assessment, ORR was 52.6% (95% CI, 40.9-64.0), with 13 CRs and 28 PRs. By independent central review, the disease control rate was 79.5% (95% CI, 68.8-87.8).

Investigators observed rapid, deep, and durable reductions in target lesions in many patients. By independent central review, median DOR, median PFS, and OS had not been reached at data cutoff. Responses have lasted  $\geq 12$  months for 12 patients. The Kaplan-Meier estimated event-free probability at 12 months in patients with confirmed CR or PR was 87.8% (95% CI, 66.7-95.9). The longest DOR at data cutoff was 24.2 months and was ongoing. The Kaplan-Meier estimated PFS at 12 months was 58.1% (95% CI, 43.7-70.0). The Kaplan-Meier estimated OS at 12 months was 93.2% (95% CI, 84.4-97.1).

In a subgroup analysis by reasons for contraindication of surgery, no differences were reported in ORR between patients with local invasion precluding complete resection ( $n = 20$ ; ORR, 50.0%) and those with anatomically challenging lesions ( $n = 30$ ; ORR, 56.7%). In patients with recurrent lesions after  $\geq 2$  surgeries, however, ORR was lower ( $n = 25$ ; ORR, 24.0%). Disease control rates in these subgroups followed a similar pattern.

Cemiplimab was active in both PD-L1 positive (TPS,  $\geq 1\%$ ;  $n = 31$ ; ORR, 54.8%) and PD-L1 negative (TPS,  $< 1\%$ ;  $n = 17$ ; ORR, 35.5%) subgroups. Among patients with samples available for analysis, median TMBs were 74.2 and 28.7 mutations per megabase, respectively, for 21 patients experiencing responses versus 29 patients not experiencing responses by independent central review.

Among 29 patients who experienced durable disease control and 21 patients who did not by independent central review, median TMBs were 64.9 and 31.5 mutations per megabase, respectively. Preliminary analysis suggests associations between high TMB and 12-month PFS and OS; however, longer follow-up is needed for more patients to reach the 12-month landmark analysis.

Grade  $\geq 3$  treatment-emergent AEs that led to treatment discontinuation included pneumonitis (2 patients)

and encephalitis, hepatitis, increased aspartate aminotransferase levels, pneumonia, and proctitis (1 each).

Treatment-related AEs (TRAEs) occurred in 62 patients (79.5%), with 10 patients (12.8%) experiencing grade  $\geq 3$  TRAEs, including pneumonitis (2 patients) and autoimmune hepatitis, death, dizziness, encephalitis, hepatitis, hypophosphatemia, increased aspartate aminotransferase levels, increased lipase levels, myocarditis, pneumonia, and proctitis (1 each).

Serious grade  $\geq 3$  TRAEs occurred in 6 patients and included pneumonitis (2 patients) and autoimmune hepatitis, death, encephalitis, myocarditis, pneumonia, and proctitis (1 each). A total of 12 grade  $\geq 3$  immune-related AEs occurred in 8 patients (10.3%), including pneumonitis (2 patients) and autoimmune hepatitis, encephalitis, hepatitis, hypophosphatemia, increased aspartate aminotransferase levels, increased lipase levels, myocarditis, pneumonia, and proctitis (1 each).

Two deaths resulting from treatment-emergent AEs related to pneumonia occurred in patients 80 years or older; 1 was considered treatment related.

The study authors concluded that cemiplimab at the dose tested has antitumor activity, with durable responses in the patient with laCSCC for whom surgical resection or radiotherapy was contraindicated. Cemiplimab had an acceptable safety profile with no new safety signals and a safety profile consistent with that of other PD-1 inhibitors.

Further prospective studies of cemiplimab in patients with advanced CSCC in both the preoperative (neoadjuvant) and postoperative (adjuvant) settings are planned. Data do not support the clinical utility of either TMB or PD-L1 expression in predicting outcome among patients with advanced CSCC treated with cemiplimab.

## Discussion

Katharine A. Price, MD, of Mayo Clinic in Rochester, Minnesota, discussed the poster, which she referred to as “practice changing.” She explained how cemiplimab compares with prior systemic therapies for CSCC. Cemiplimab has the highest response rate compared with past treatments of cytotoxic chemotherapy and epidermal growth factor receptor inhibition, and the PFS is 3 to 4 times that of other therapies.<sup>7</sup>

TMB is a potential biomarker for immunotherapy, and skin cancers have been targeted with immunotherapy for this reason. In this study, however, investigators observed only a slight enrichment for response at high TMB levels. At the 2018 ASCO Annual Meeting, data were presented indicating that PD-L1 staining correlated with response to

checkpoint inhibition for CSCC.<sup>8</sup> Looking at the trials for both metastatic and locally advanced disease, the response rate is a bit higher in PD-L1 positive tumors, ranging from 42% to 66%. Notably, however, one-third of patients with CSCC have tumor responses to cemiplimab, suggesting that these drugs should not be limited to treatment of PD-L1 positive tumors.

“Perhaps the most interesting aspect of this study is the differing response rate by patient eligibility,” Price said. In patients who were eligible for the trial because they had an unresectable tumor or because they had a tumor that was resectable, but for which surgery would result in unacceptable morbidity, the response rate to cemiplimab was very high—more than 50% in both cases. However, for patients who had  $>2$  surgeries at the same site, the response rate was 24%. Price said this finding raises questions about the tumor microenvironment in the setting of a site treated with prior surgery. Surgery has been shown to generate an immunosuppressive environment with an increase in T regulatory cells, proinflammatory cytokines, and a decrease in CD8-positive cells, all of which could explain an attenuated response to cemiplimab.

Although cemiplimab is approved for the treatment of patients with locally advanced and metastatic CSCC, this differing response raises the further question of when these agents should be administered and challenges some of the standard treatment approaches in oncology for laCSCC, in which customary practice is to exhaust local therapies first. These data suggest that cemiplimab could potentially be administered earlier in the disease course.

## Conclusions

Cemiplimab for the treatment of laCSCC replicates responses seen in patients with distant metastases. This is the highest response rate and longest duration of response seen in this population to date, Price said, and represents a new standard of care. The decreased response rate after 2 surgical procedures suggests earlier use in the disease course, and this is the subject of ongoing preoperative trials.

As in many immunotherapy trials, patients who have undergone transplants and immunosuppressive therapy are often excluded, which still represents an area of dire unmet need. Regarding deaths in patients of advanced age, Price noted, “I think we don’t entirely understand the safety of these drugs in patients in that age range.”

Finally, Price suggested that PD-L1 alone is insufficient as a biomarker for CSCC. Understanding tumor

microenvironment is critical for the development of novel and more effective immunotherapy combinations. Data from this trial support moving checkpoint inhibitor therapy earlier in the treatment course. ♦

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## Ribociclib Improves Survival by Nearly 30% for Premenopausal Women With Advanced Breast Cancer

(continued from cover)

findings from the phase 3 MONALEESA-7 trial that were simultaneously published in the *New England Journal of Medicine* and presented at the 2019 American Society of Clinical Oncology (ASCO) Annual Meeting.<sup>1,2</sup>

The improvement in OS rate represented a 29% reduction in the risk of death with the addition of the cyclin-dependent kinase (CDK) 4/6 inhibitor to endocrine therapy (hazard ratio, 0.71; 95% CI, 0.54-0.95;  $P = .00973$ ). The 42-month progression-free survival (PFS) rate was 54.6% with ribociclib compared with 37.8% with placebo, representing a 31.0% reduction in the risk of progression or death with the combination (hazard ratio, 0.69; 95% CI, 0.55-0.87).

“This is the first time a statistically significant improvement in [OS] has been observed with a CDK4/6 inhibitor in combination with endocrine therapy in patients with HR-positive, HER2-negative advanced breast cancer,” lead study author Sara A. Hurvitz, MD, director of the Breast Cancer Clinical Trials Program at the University of California, Los Angeles, Jonsson Comprehensive Cancer Center, said during an early presentation of the findings. “It’s important to note that it is very difficult in metastatic breast cancer studies to demonstrate a significant improvement in [OS] because patients have

the opportunity to receive subsequent treatments after coming off trial.”

In 2017, the FDA initially approved ribociclib in combination with an aromatase inhibitor for postmenopausal women with HR-positive, HER2-negative advanced breast cancer. In July 2018, the FDA expanded this indication to include pre- and perimenopausal women with the disease, based on an earlier assessment of PFS from the MONALEESA-7 study. The median PFS was 27.5 months with ribociclib compared with 13.8 months for placebo (hazard ratio, 0.569; 95% CI, 0.436-0.743).

The MONALEESA-7 trial enrolled 672 pre- or perimenopausal women with advanced breast cancer to receive endocrine therapy with ribociclib ( $n = 335$ ) or placebo ( $n = 337$ ). Ribociclib was administered at 600 mg once daily for 21 days followed by 7 days without the CDK4/6 inhibitor. Endocrine therapy consisted of a nonsteroidal aromatase inhibitor (NSAI;  $n = 495$ ) or tamoxifen ( $n = 177$ ), based on the patient’s previous adjuvant or neoadjuvant therapy or preference. The use of these therapies was evenly balanced across each arm. Subcutaneous goserelin was administered to patients in both groups at 3.6 mg on day 1 of each cycle.

Overall, 68.9% and 73.2% of patients went on to receive subsequent therapy in the ribociclib and placebo groups, respectively. The therapies received were similar between the arms and consisted of chemotherapy alone (22.4% and 28.6% for ribociclib and placebo, respectively), hormone therapy alone (22.4% and 20.4%, respectively), hormone therapy plus other therapy (14.2% and 14.6%), chemotherapy plus hormone therapy or other therapy (8.2% and 7.9%), and other therapies (1.8% each). Overall, 10.0% of patients in the ribociclib arm and 18.6% of patients in the placebo group received a subsequent CDK4/6 inhibitor (palbociclib, abemaciclib, or ribociclib if they were in the placebo group).

At the 42-month analysis, median OS was not estimable in the ribociclib arm compared with 40.9 months in the placebo group. The median PFS was 23.8 months with ribociclib compared with 13.0 months with placebo (hazard ratio, 0.55; 95% CI, 0.44-0.69;  $P < .0001$ ).

## [T]hese outcomes suggest that patients with advanced CSCC tumors, whether metastatic or locally advanced, derive durable clinical benefit from cemiplimab.

The 42-month OS analysis reached a predefined efficacy stopping boundary, making these data the final OS analysis for the study. Prior OS analyses from the study showed an OS advantage for ribociclib beginning at 24 months. The 24-month OS rate was 82.7% in the ribociclib arm compared with 81.8% for placebo; however, by month 36 the Kaplan-Meier curves began to separate, with an OS rate of 71.9% in the ribociclib arm compared with 64.9% with placebo.

When analyzing subgroups by type of endocrine therapy, investigators observed the greatest benefit in patients receiving an NSAI. In this group, 248 patients received ribociclib and 247 were administered placebo. A statistically significant 30% reduction in the risk of death was observed with the addition of ribociclib

(hazard ratio, 0.70; 95% CI, 0.50-0.98). The estimated OS rate at 42 months was 69.7% with ribociclib compared with 43.0% for placebo.

In the tamoxifen subgroup, investigators observed there was a nonstatistically significant 21% reduction in the risk of death with ribociclib (hazard ratio, 0.79; 95% CI, 0.45-1.38). Patient numbers were small in this cohort, with 87 patients in the ribociclib arm and 90 in the placebo group. The 42-month OS rate was 71.2% with ribociclib compared with 54.5% with placebo.

“This is a smaller subgroup. We actually do not give tamoxifen with ribociclib. Subsequent to this study closing, it was determined that tamoxifen is associated with prolongation of the QT interval, so it could put patients at risk for arrhythmia. [Ribociclib] is not approved in combination with tamoxifen,” said Hurvitz.

Commenting on the findings in a statement released by ASCO prior to the presentation of the data, expert Harold J. Burstein, MD, PhD, associate professor of medicine at Harvard Medical School in Boston, Massachusetts, said that “advanced breast cancer in premenopausal women can be very aggressive. It is important and encouraging to see a targeted therapy that significantly increases survival for younger women with this disease.

“In an era when we are thinking about value in oncology care, the demonstration of a robust survival benefit adds to the value proposition for products like ribociclib,” said Burstein. “So, hopefully, these data will enable access to this product to more women around the world, particularly in healthcare systems that assess value more rigorously as part of their decisions for national access to their drugs.”

Investigators are exploring ribociclib in earlier settings for patients with HR-positive, HER2-negative breast cancer. The phase 3 NATALEE trial is examining the CDK4/6 inhibitor as an adjuvant therapy in combination with endocrine therapy for patients with early breast cancer. The primary end point of the study is invasive disease-free survival, and the estimated primary completion date is December 2025 (NCT03701334). ♦

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# Cemiplimab in Metastatic Cutaneous Squamous Cell Carcinoma Shows Promise in Phase 2 Study

Lynne Lederman, PhD

**NEW FINDINGS PRESENTED AT** the 2019 American Society for Clinical Oncology Annual Meeting (ASCO) indicate that cemiplimab-rwlc confers durable clinical benefits to patients with metastatic cutaneous squamous cell carcinoma (CSCC). EMPOWER-CSCC-1 (NCT02760498) is a phase 2 study that evaluated cemiplimab-rwlc, a human monoclonal anti-programmed cell death (PD) 1 antibody, in patients with metastatic CSCC. Alexander D. Guminski, PhD, Department of Medical Oncology, Royal North Shore Hospital, St Leonards, Australia, reported 12-month follow-up results for EMPOWER-CSCC-1 in a poster session.<sup>1</sup>

Although CSCC is second only to basal cell carcinoma in incidence in the United States<sup>2</sup> and is one of the most common cancers worldwide,<sup>3</sup> no approved systemic therapy for advanced CSCC, which includes metastatic and locally advanced CSCC, was available in the United States until the recent FDA approval of cemiplimab-rwlc.

Cemiplimab-rwlc is the only FDA-approved treatment for patients specifically with metastatic CSCC or locally advanced CSCC who are not candidates for curative surgery or curative radiation.<sup>4</sup> It is a recombinant human immunoglobulin G4 monoclonal antibody that binds to the PD-1 receptor, blocking the interactions of PD-ligand 1 and PD-ligand 2.<sup>4</sup> Primary analysis of the EMPOWER-CSCC-1 trial of cemiplimab in patients with metastatic CSCC showed significant antitumor activity, durable response, and a tolerable safety profile.<sup>1,5</sup>

## Data Analysis

Presented in the 12-month follow-up, adult patients with metastatic nodal and/or distant CSCC were enrolled in group 1. The 59 patients enrolled received cemiplimab 3 mg/kg every 2 weeks by intravenous infusion for up to 96 weeks. Retreatment was optional for patients who had disease progression throughout follow-up. The data cutoff date was September 20, 2018. The median duration of follow-up was 16.5 months.<sup>1</sup>

The primary end point of the phase 2 study was objective response rate (ORR; complete response [CR] plus partial response [PR]). Tumor imaging was performed every 8 weeks to assess efficacy.<sup>1</sup> Among the secondary end points were ORR by investigator assessments, duration of response (DOR), progression-free survival (PFS), overall survival (OS), and durable disease control rate (ie, the proportion of patients without progressive disease for at

least 105 days). Investigators used the National Cancer Institute Common Terminology Criteria for Adverse Events as the grading system for treatment-emergent adverse events (TEAEs).<sup>1</sup>

The median age of the patient population was 71 years; 54% were male, and about 61% had an Eastern Cooperative Oncology Group performance status of 1. The primary CSCC site was head/neck in 64.4% of patients, an extremity in 20.3%, and the trunk in 15.3%. Distant metastases were reported in 76.3% of patients and nodal metastasis in 23.7%.<sup>1</sup> Approximately half of patients (55.9%) had received prior cancer-related systemic therapy, and most (84.7%) had received prior cancer-related radiotherapy.<sup>1</sup>

At the time of cutoff, 22.0% of patients had completed arranged treatment, 22.0% remained on treatment, and 55.9% had discontinued treatment primarily because of disease progression, AEs, or CR to cemiplimab.<sup>1</sup> Through independent central review, ORR was 49.2% (95% CI, 35.9-62.5); CR was observed in 10 patients, and 19 patients underwent a PR. Investigator assessment of ORR was 49.2% (95% CI, 35.9-62.5), with 4 CRs and 25 PRs.<sup>1</sup>

Treatment with cemiplimab was associated with rapid, deep, and durable responses. By independent central review, the median DOR was not reached at the time of data cutoff. The longest DOR at data cutoff was 21.6 months and was ongoing. Twenty-two patients experienced responses for  $\geq 12$  months. The event-free probability at 12 months in patients with confirmed CR or PR was estimated at 88.9% (95% CI, 69.3-96.3).<sup>1</sup> Median PFS was 18.4 months (95% CI, 7.3-not evaluable). Median OS was not reached, and the Kaplan-Meier OS estimation at 24 months was 70.6% (95% CI, 57.0-80.6).

Grade 3 or treatment-emergent AEs were observed in 50.8% of patients. Serious AEs (SAEs) of any grade were observed in 40.7% of patients, with grade  $\geq 3$  SAEs in 33.9% of patients. More than 1 patient experienced cellulitis (6.8%); pneumonitis (5.1%); and anemia, dyspnea, hypercalcemia, new primary CSCC, pleural effusion, and pneumonia (2 each, 3.4%) as grade  $\geq 3$  TEAEs.<sup>1</sup>

TEAEs of any grade led to discontinuation in 6 patients, in whom 4 were grade  $\geq 3$ . Pneumonitis (n = 3; 5.1%) and aseptic meningitis, state of confusion, and neck pain (all in the same patient) were grade  $\geq 3$  TEAEs that led to treatment discontinuation.<sup>1</sup>

Treatment-related (TR) AEs were present in 46 patients (78.0%), and 9 patients (15.3%) experienced pneumonitis (5.1%) and aseptic meningitis, colitis, confusional state, decreased lymphocyte count, diarrhea, duodenal ulcer, esophagitis, hypophysitis, neck pain, polyarthrititis, and small intestinal hemorrhage (1 each, 1.7%) as grade  $\geq 3$  TRAEs.<sup>1</sup> Serious grade  $\geq 3$  TRAEs were observed in 6 patients (10.2%), including pneumonitis, aseptic meningitis, duodenal ulcer, hypophysitis, esophagitis, and small intestine hemorrhage.<sup>1</sup>

Eight patients (13.6%) experienced a total of 11 grade  $\geq 3$  immune-related AEs, including pneumonitis, polyarthrititis, aseptic meningitis, colitis, state of confusion, diarrhea, decreased lymphocyte count, hypophysitis, and neck pain. Three patients were previously reported<sup>5</sup> to have TEAEs considered unrelated to study treatment that resulted in death. During this 12-month follow-up analysis, no new TEAEs resulting in death occurred.<sup>1</sup>

### Conclusions

The results of this phase 2 study suggest that cemiplimab administered at 3 mg/kg twice weekly shows considerable antitumor activity, with increased DOR in patients with metastatic CSCC. Median duration of response was not reached. Among patients whose CSCC responded to treatment, the estimated 12-month DOR was 88.9%. This dose and schedule of cemiplimab also had a tolerable safety profile, with no new safety signals compared with the primary analysis.<sup>5</sup> In combination with a separate phase 2 primary analysis of patients with

locally advanced CSCC (group 2) presented at the 2019 ASCO Annual Meeting,<sup>6</sup> these outcomes suggest that patients with advanced CSCC tumors, whether metastatic or locally advanced, derive durable clinical benefit from cemiplimab.<sup>1</sup> ♦

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## Niraparib/Bevacizumab Combo Active in Recurrent Ovarian Cancer

A **CHEMOTHERAPY-FREE DOUBLET** for platinum-sensitive recurrent ovarian cancer (PSROC) more than doubled progression-free survival (PFS) compared with a single-agent poly (ADP-ribose) polymerase (PARP) inhibitor, results of a randomized trial showed.

Patients randomized to niraparib (Zejula) plus bevacizumab (Avastin) had a median PFS of 11.9 months versus 5.5 months for those taking niraparib alone. Patients with a prior platinum-free interval (PFI) of 6 to 12 months or >12 months derived similar benefit from the combination regimen.

Niraparib and bevacizumab also proved active in patients with or without homologous recombination deficiency (HRD) and those with or without *BRCA* mutations, according to results presented at the 2019 American Society of Clinical Oncology Annual Meeting.<sup>1</sup>

“[This study] is the first randomized trial to evaluate a chemotherapy-free combination of 2 established agents approved for use in recurrent ovarian cancer,” said Mansoor R. Mirza, MD, of Copenhagen University Hospital in Denmark. “Compared with niraparib alone, the combination of niraparib and bevacizumab as

definitive treatment for ovarian cancer significantly improved progression-free status regardless of HRD status or chemotherapy-free interval.

“The combination was well tolerated, and most patients remained on treatment until disease progression. No detrimental effect on quality of life was observed with combination therapy,” Mirza said.

A planned randomized phase 3 trial will compare the combination with standard-of-care therapy for PSROC, Mirza added.

## [This study] is the first randomized trial to evaluate a chemotherapy-free combination of 2 established agents approved for use in recurrent ovarian cancer.

Platinum-based chemotherapy remains standard of care for PSROC, but its use is limited by cumulative toxicity. In the phase 3 NOVA trial, niraparib maintenance following platinum-based chemotherapy significantly improved PFS without adversely affecting sensitivity to subsequent therapy.<sup>2</sup> Single-agent niraparib also proved active as definitive treatment for relapsed ovarian cancer.<sup>3</sup>

Mirza reported findings from the AVANOVA randomized phase 2 trial to evaluate PARP inhibition and antiangiogenesis as alternative strategies to platinum-based chemotherapy. The rationale for the combination included observations that tumor hypoxia induced by antiangiogenic agents enhanced PARP inhibition.

Investigators from the Nordic Society of Gynaecological Oncology enrolled patients with high-grade serous or endometrial PSROC and any number of prior lines of therapy. Patients were randomized to niraparib alone at 300 mg once daily or to the same dose of the PARP inhibitor plus bevacizumab 15 mg/kg every 3 weeks. Treatment continued until disease progression or development of unacceptable toxicity. The primary end point was investigator-assessed PFS in the intention-to-treat population.

Data analysis included 97 randomized patients, and the median age was 66 years. Approximately 40% of the patients had a PFI of 6 to 12 months, and the interval exceeded 12 months in the remaining patients. About 60% of patients tested positive for HRD, and a third had *BRCA*-mutant disease.

The primary analysis showed a 6.4-month improvement in median PFS with the combination, representing a 65% reduction in the hazard for disease progression or death ( $P < .0001$ ). The advantage conferred by the combination was similar for patients with a PFI of 6 to 12 months (11.3 vs 2.2 months,  $P = .0006$ ) or >12 months (13.1 vs 6.1 months,  $P = .0062$ ) and patients with HRD-positive tumors (11.9 vs 6.1 months,  $P = .0019$ ) or HRD-negative tumors (11.3 vs 4.2 months,  $P = .0129$ ). The combination offered a numerical advantage to patients with *BRCA*-mutant tumors (14.4 vs 9.0 months,  $P = .0947$ ) and a statistically significant advantage to patients with *BRCA* wild-type tumors (11.3 vs 4.2 months,  $P = .0001$ ).

The odds ratio (OR) for objective response quadrupled with the combination (60% vs 27%; OR, 4.23;  $P = .001$ ), and the odds of achieving disease control more than tripled (79% vs 53%; OR, 3.36;  $P = .008$ ).

Patients randomized to the combination experienced more adverse events, particularly nausea, vomiting, hypertension (associated with bevacizumab), peripheral neuropathy, and proteinuria. Severity was grade 1/2 in most cases, except for a 20% incidence of grade  $\geq 3$  hypertension.

An assessment of global health quality and quality of life over time showed no deterioration in either treatment group and no significant differences between the groups. ♦

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# REGN3767, a Human LAG-3 Monoclonal Antibody, With or Without Cemiplimab Demonstrates Antitumor Activity in Patients With Advanced Malignancies

Lynne Lederman, PhD

## AN INVESTIGATIONAL HUMAN LYMPHOCYTE-ACTIVATION

gene 3 (LAG-3) monoclonal antibody, REGN3767, appears to exhibit broad antitumor activity across advanced malignancies, new findings suggest. In an oral session at the 2019 American Society of Clinical Oncology (ASCO) Annual Meeting, Kyriakos P. Papadopoulos, MD, South Texas Accelerated Research Therapeutics, San Antonio, Texas, presented the results of a phase 1, open-label, dose-escalation study of REGN3767, with and without cemiplimab, for the treatment of patients with advanced malignancies (NCT03005782).<sup>1</sup>

LAG-3 is an immune checkpoint receptor that delivers inhibitory signals to activated T cells upon ligand binding.<sup>2</sup> It is upregulated in tumor-infiltrating T cells in many types of cancer.<sup>3</sup> LAG-3 is associated with significant therapeutic resistance to anti-programmed cell death 1 (PD-1) agents,<sup>4</sup> suggesting that immunosuppressive activity of LAG-3 may be complementary to that of PD-1.

REGN3767 and cemiplimab are high-affinity, human, hinge-stabilized immunoglobulin G4 antibodies to LAG-3 and the PD-1 receptor, respectively. REGN3767 blocks LAG-3 and cemiplimab blocks the interaction between PD-1 and its ligands.<sup>1,5,6</sup>

## Data Analysis

In a dual-humanized PD-1/LAG-3 mouse model, REGN3767 alone and in combination with cemiplimab exhibited encouraging antitumor activity, providing the preclinical rationale for the current study.<sup>1</sup>

The primary objective of this first-in-human study of REGN3767 was to evaluate the safety and pharmacokinetics (PK) of REGN3767 monotherapy and combination therapy with cemiplimab, to determine the dose level(s) needed for expansion. The study also examined preliminary antitumor activity and pharmacodynamics (PD). Tumor responses were assessed every 6 weeks for the first 24 weeks, then every 9 weeks thereafter.

Doses of REGN3767 were escalated from 1 to 20 mg/kg every 3 weeks in 3 + 3 cohorts, which were modified for additional patients to evaluate tolerability. Cemiplimab was administered at 3 mg/kg every 3 weeks, along with REGN3767 at 1 mg/kg, 3 mg/kg, or 10 mg/kg; or at 350

mg intravenously every 3 weeks, along with REGN3767 at 10 mg/kg or 20 mg/kg.<sup>1</sup> Patients in the REGN3767 monotherapy arm who experienced disease progression but were otherwise stable without toxicity were allowed to cross over to combination therapy.

Patients with lymphoma were allowed to enter the study. Patients with an autoimmune disease and prior anti-LAG-3 exposure were excluded from the study. A total of 69 patients were enrolled, 27 in the monotherapy arm and 42 in the combination therapy arm; 13 patients crossed over from monotherapy to combination therapy at clinical or radiologic progression. Ages ranged from 22 to 83 years, with a median of 66 years.<sup>1</sup>

The most common tumor type was colon cancer. Other tumor types included lung, biliary tract, ovarian, and pancreatic and were considered predominantly immunologically cold. About one-third of the patients had received prior radiotherapy. Previous exposure to PD-1 was reported among patients in the combination arm. Almost all patients have discontinued therapy, with disease progression the most common reason for discontinuation. Overall, 4 deaths occurred in the monotherapy arm, and 3 deaths occurred in the combination arm, although none of the deaths were attributed to the treatment. No discontinuations due to adverse events (AEs) were reported. One patient is continuing the treatment. Median drug exposure ranged from 9 to 16 weeks, with a median number of doses of 3 to 6, depending on the cohort.

The incidence of immune-related AEs was low in patients in the REGN3767 monotherapy group. Other AEs included abdominal pain, decreased appetite, diarrhea, fatigue, nausea, and vomiting. Transaminitis with a 3-mg/kg dose of REGN3767 was reported in 1 patient with liver metastases, who subsequently died of hepatic failure that was considered unrelated to the study drug. No dose-limiting toxicities (DLTs) were reported. The maximum tolerated dose was not established, and the multiple ascending dose (MAD) was 20 mg/kg.

Treatment-emergent AEs in the combination arm reflect the safety profile of cemiplimab. Overall, 3 patients had grade 3 immune-related toxicities. Among these, 1 DLT was reported in a patient with grade 3 myasthenia syndrome with elevated creatine phosphokinase and

troponin levels. Of the 2 additional patients, one had hypothyroidism and the other had diabetic ketoacidosis with type 1 diabetes. One patient died because of sepsis, which was unrelated to the study drug.

In the crossover from monotherapy to the combination therapy arm, no DLTs were reported. The MAD was confirmed as REGN3767 at 20 mg/kg and cemiplimab at 350 mg/kg. Grade 3 AEs occurred in 3 patients who had been on treatment for >1 year, 1 with pruritus and pneumonitis, 1 with rash, and 1 with adrenal insufficiency. These AEs resolved with supportive care. One patient discontinued treatment because of pneumonitis.

PK results demonstrated a dose-dependent increase in REGN3767 concentration and no interaction with cemiplimab. The half-life of REGN3767 was approximately 21 days. PD results indicated no proliferative change in either CD4 or CD8 cells with REGN3767 monotherapy. An apparent dose-dependent increase in proliferative change occurred in both CD4 and CD8 effector cells, however, with increasing doses of the combination therapy.

No responses were observed with monotherapy. Two partial responses were reported, each in the combination (4.8%) and crossover (16.7%) groups, with 1 patient and 2 patients, respectively, experiencing an ongoing response. In the monotherapy group, 48% of patients experienced stable disease.

Papadopoulos concluded that REGN3767 plus cemiplimab has an acceptable safety profile in patients with advanced malignancies. No new safety signals with monotherapy or combination therapy were reported. The PKs were predictable and dose dependent. No PD effect on effector cells with REGN3767 monotherapy was reported, but a trend toward increasing effector cells in combination with cemiplimab was observed. Some efficacy signals were reported in this dose-escalation study. REGN3767 at 20 mg/kg, or a 1600-mg fixed dose every 3 weeks, in monotherapy or in combination, has been selected for further evaluation and expansion cohorts.<sup>1</sup>

## Discussion

Sanjay Goel, MD, of Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, New York, discussed this abstract, along with 2 others in the session, in a presentation entitled “Expanding the Horizon of Rational Immunotherapy Combinations.” Noting that 3 immuno-oncology (IO) combinations and 5 IO plus non-IO combinations have already been approved in the United States, Goel queried, “Why do we need immunotherapy combinations with other immunotherapy drugs?” Combinations could activate these

agents in a suppressed pathway or suppress immune inhibitory pathways in ways that might be complementary. Possibly, doses could be lowered, thus reducing toxicities. Immune escape and immune resistance mechanisms could be targeted. Most important, the median overall survival could be improved, which Goel referred to as an elusive target to date.

As with PD-1 and programmed death-ligand 1, because LAG-3 is overexpressed in suppressed T cells, investigators believe that overcoming the interaction of LAG-3 with major histocompatibility complex may allow the checkpoint inhibitors to synergize.

Although no PK interactions were detected between REGN3767 and cemiplimab, as reported by Dr. Papadopoulos, a PD effect of Ki-67 positivity in the PD-1 subset of both CD4 and CD8 may exist. This may prompt the question of whether sequential dosing matters, particularly because more responses were reported in the group who crossed over from monotherapy to combination therapy than in the combination therapy group, although these numbers were small. The small number of responses was encouraging nonetheless.

Goel commented, “This [raises] the question, Does targeting LAG-3 initially prime the tumor to subsequent combination checkpoint inhibition? One concern, though, is a very high rate of grade 3 toxicities that exceed 40%. So we need to figure out some plans to manage this or mitigate these in further trials. Lastly, how do we incorporate the increase in PD-1–positive Ki-67 CD8 cells as a potential biomarker for further development?”

According to Goel, one aspect of the trial that could be improved is the recruitment of minorities, as 85% to 89% of the patients in the 3 treatment groups were white. Goel noted that the US population is 77% white and 60% non-Hispanic white. Additionally, he predicted that the cost of these combination treatments will likely exceed \$250,000 annually. The toxicities appear to be manageable, although some are of concern.

In addition, Goel pointed out that 2 major failures of IO therapy should provide a word of caution. One was the combination of nivolumab plus ipilimumab for the treatment of patients with non–small cell lung cancer (NSCLC), with the investigators suggesting that the use of a tumor mutational burden cutoff of  $\geq 10$  mutations per megabase would be a predictive biomarker for efficacy in NSCLC.<sup>7</sup> Additional follow-up, however, showed no survival benefit, leading to the sponsor’s withdrawal of the application from the FDA.<sup>8</sup> The underlying issue is unknown: Was the problem that the trial used an incorrect biomarker or that it addressed the wrong therapeutic target? Or, as Goel indicated, “Is it incomplete science?”

The second trial to offer a cautionary signal included the failure of treatment with epacadostat plus pembrolizumab. Epacadostat targets indoleamine 2,3-dioxygenase 1, another immune checkpoint molecule. The early results of the phase 1/2 trial were encouraging,<sup>9</sup> leading to the launch of a phase 3 trial in patients with advanced melanoma. Unfortunately, as presented at the 2018 ASCO Annual Meeting, this combination therapy did not demonstrate any survival benefit.<sup>10</sup>

## Conclusions

Regarding strategies for future development, investigators need a clearer focus and commitment to identify biomarkers in early-stage trials. Rational trial designs and scientifically driven entry criteria in later-stage trials are also necessary. Goel concluded, “We need commitment by industry to keep costs reasonable, and [to] enhance and require minority accruals in all stages of trials, so that we walk the walk rather than simply providing lip service.” ♦

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# Acalabrutinib Combination Induces High Responses in CLL

**SIMULTANEOUS TARGETING OF BRUTON** tyrosine kinase (BTK) and the CD20 antigen led to overall responses in more than 90% of patients with chronic lymphocytic leukemia (CLL), including untreated and relapsed/refractory disease, according to results from a small preliminary trial.<sup>1</sup>

Patients with previously untreated disease had an overall response rate (ORR) of 95%, declining slightly to 92% in patients with relapsed/refractory CLL when treated with the combination of acalabrutinib (Calquence) and obinutuzumab (Gazyva). Median duration of response was yet to be reached.

Patients with no prior treatment had a 39-month progression-free survival (PFS) rate of 94.4%, and those with previously treated disease had a 42-month PFS rate of 72.7%, according to results reported at the 2019 American Society of Clinical Oncology Annual Meeting.

“Treatment with acalabrutinib plus obinutuzumab yielded high response rates that were durable and deepened over time in both relapsed/refractory and treatment-naïve patients,” said Jennifer Woyach, MD, of The Ohio State University Comprehensive Cancer Center in Columbus. “This combination was well tolerated in both cohorts, with low rates of grade  $\geq 3$  adverse events [AEs] and grade  $\geq 3$  bleeding and only 1 case of atrial fibrillation. Most patients remain on treatment after a median follow-up of 3.5 years.”

BTK has an essential role in B-cell receptor signaling and has become a validated therapeutic target for CLL. In phase 1/2 clinical trials, the BTK inhibitor acalabrutinib achieved ORRs exceeding 90% as a single-agent therapy for patients with untreated and relapsed/refractory CLL.<sup>2-4</sup> Obinutuzumab has approved indications for follicular lymphoma and untreated CLL.

Woyach reported findings from the 3-year follow-up of a single-arm trial involving 45 patients with CLL, 19 with untreated disease, and 26 with relapsed/refractory CLL. In the group with relapsed/refractory disease, prior treatment with a BTK inhibitor was allowed except in the case of discontinuation for on-treatment disease progression.

The study population had a median age of about 62, half had bulky disease, and only 1 patient had small lymphocytic lymphoma. About 20% had deletion (del) 17p, a third had del(11q), most had unmutated *IGHV*, and about half had complex karyotype.

After a median follow-up of about 3.5 years, 78% of the patients remained on treatment. Woyach noted that 10 patients discontinued acalabrutinib, 5 because of AEs, 4 because of Richter transformation, and 1 because of

disease progression, and 1 patient died. All but 2 patients completed treatment with obinutuzumab.

The ORR in patients with previously untreated CLL consisted of complete responses (CRs) in 31.6% of patients and partial responses (PRs) in 63.2%. In the relapsed/refractory group, 7.1% of patients had CRs and 84.8% had PRs.

Woyach added that the CR rate increased from 15% after 22 months, reflecting conversion from partial to CRs in 3 patients. The median time to CR was 18 months in the untreated patients and 12 months in the relapsed/refractory group. Median duration of response had yet to be reached in either group. At last follow-up visit, duration of response exceeded 90% in patients with untreated and relapsed/refractory disease.

Regarding minimal residual disease (MRD) status, 26% of previously untreated patients had MRD  $\leq 0.01\%$ , 21% had MRD  $>0.01\%$  to  $<0.1\%$ , and 42% had MRD  $>1.0\%$ . One patient in the untreated cohort discontinued treatment compared with none in the relapsed/refractory group.

The most common AEs (all grades) were upper respiratory tract infections (73%), weight gain (72%), maculopapular rash (66%), cough (64%), diarrhea (64%), headache (56%), nausea (54%), arthralgia (46%), dizziness (46%), constipation (45%), contusion (42%), fall (42%), infusion-related reaction (42%), sinusitis (42%), vomiting (42%), and fatigue (40%). The most common grade  $\geq 3$  AEs were neutropenia (24%); syncope (11%); decreased platelet count, cellulitis, and weight gain (9% each); and hypertension and hypophosphatemia (7% each). ♦

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# Patterns of Major Surgeries Among Patients With Cutaneous Squamous Cell Carcinoma Elucidated

Lynne Lederman, PhD

**SYSTEMIC THERAPY DOES NOT** decrease the likelihood of surgery in patients with cutaneous squamous cell carcinoma (CSCC), new findings suggest. Investigators at Regeneron Pharmaceuticals, Inc, the Department of Dermatology of Brigham and Women's Hospital, and Harvard Medical School evaluated patterns of major surgeries in patients with CSCC, the second-most-common skin cancer, for a publication-only abstract presented at the recent annual meeting of the American Society of Clinical Oncology.<sup>1</sup> Among those evaluated were individuals requiring systemic therapy.<sup>1</sup>

The American Cancer Society reports that although skin cancer is the most commonly diagnosed cancer in the United States, the concrete number of the most common forms, including CSCC, is challenging to estimate because clinicians are not required to report cases to cancer registries. When diagnosed early, CSCC can be cured via surgical excision or by removing the lesion via other techniques.<sup>2</sup>

This study identified initial diagnoses of patients with CSCC in Truven MarketScan claims data between 2013 and 2018. Participants in the study were continuously enrolled in their healthcare plan with no diagnosis of CSCC in the prior 12 months. The main surgeries evaluated included facial excisions over 3.1 cm, parotidectomy, removal of ear/eye/nose, amputations, craniectomy, excision of extracranial nerves, sentinel lymph node biopsy, lymphadenectomy, complex repairs of over 7.5 cm, integra, free flaps, and large grafts over 20 square cm.<sup>1</sup>

The investigators evaluated risk of a major surgery using Kaplan-Meier estimators for total patients with CSCC, as well as for those who received previous or concurrent systemic therapy. Patients were classified by immune status.<sup>1</sup>

The study included 240,122 patients with CSCC. Patients had a mean age of 67.7 years (SD, 12.9 years). Approximately half of the patients (56.5%) were male, and 12.4% were immunocompromised. Mean follow-up was 1.34 years (SD, 1.15 years).

Investigators found that the risk of major surgery at 1 year and 2 years was 15.1% (95% CI, 14.9-15.2) and 18.6% (95% CI, 18.4-18.8), respectively. A total of 782 patients had received prior or concurrent systemic therapy, among whom 22.4% (n = 175) were immunocompromised. For patients who received systemic therapy, the risk of major surgery at 1 year and at 2 years was 8.4% (95% CI, 5.8-11.0) and 14.2% (95% CI, 10.0-18.2), respectively, for immunocompetent patients, and 14.1% (7.7-20.0) and 19.3% (10.7-27.0) for immunocompromised patients, respectively.<sup>1</sup>

The authors concluded that approximately 1 in 5 patients with CSCC will undergo at least 1 major surgery over a period of 2 years, and the risk of undergoing major surgery did not decrease from treatment with systemic therapy. Among patients who received systemic therapy, those who were immunocompromised had a higher risk of major surgery compared with immunocompetent patients at both time points analyzed.<sup>1</sup> ♦

## REFERENCES

- Chen CI, Jalbert JJ, Andria M, et al. Patterns of major surgeries among patients diagnosed with cutaneous squamous cell carcinoma (CSCC). *J Clin Oncol*. 2019;37(suppl 15; abstr e21034). doi: 10.1200/JCO.2019.37.15\_suppl.e21034.
- Facts & figures 2019. American Cancer Society website. [cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2019/cancer-facts-and-figures-2019.pdf](https://cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2019/cancer-facts-and-figures-2019.pdf). Published 2019. Accessed June 11, 2019.



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# Ramucirumab/Erlotinib Significantly Improves PFS in Frontline *EGFR*+ NSCLC

Jason M. Broderick

**ADDING RAMUCIRUMAB (CYRAMZA)** to erlotinib (Tarceva) reduced the risk of disease progression or death by more than 40% versus erlotinib alone as a frontline treatment for patients with *EGFR*-positive non-small cell lung cancer (NSCLC), according to findings from the phase 3 RELAY trial presented at the 2019 American Society of Clinical Oncology (ASCO) Annual Meeting.<sup>1</sup>

At a median follow-up of 20.7 months, the median progression-free survival (PFS) by investigator assessment was 19.4 months (95% CI, 15.4-21.6) with the ramucirumab combination compared with 12.4 months (95% CI, 11.0-13.5) with erlotinib alone (hazard ratio [HR], 0.591; 95% CI, 0.461-0.760;  $P < .0001$ ).

When presenting the data at the ASCO meeting, lead study author Kazuhiko Nakagawa, MD, PhD, said the median PFS for the ramucirumab combination was comparable to the median PFS with osimertinib (Tagrisso) in the pivotal phase 3 FLAURA trial that led to the FDA approval of the third-generation tyrosine kinase inhibitor (TKI) for frontline *EGFR*-positive NSCLC.

The PFS benefit with the ramucirumab combination in the RELAY trial was observed across several key subgroups, including *EGFR* mutation type. Among patients with exon 19 deletion, the median PFS was 19.6 months with the combination versus 12.5 months with erlotinib alone (HR, 0.651; 95% CI, 0.469-0.903). Among patients with exon 21 L858R, the median PFS was 19.4 versus 11.2 months, respectively (HR, 0.618; 95% CI, 0.437-0.874).

“The RELAY regimen is a new treatment option for initial treatment of *EGFR*-mutated metastatic NSCLC,” said Nakagawa, of the Department of Medical Oncology, Kindai University Faculty of Medicine, Osaka-Sayama, Osaka, Japan.

Nakagawa explained that there is an “unmet need for treatment options that extend *EGFR* [epidermal growth factor receptor] TKI efficacy,” adding that prior research supports dual blockade of vascular endothelial growth factor (VEGF)/*EGFR* signaling pathways in *EGFR*-positive NSCLC. This led Nakagawa et al to explore the combination of the *EGFR* TKI erlotinib with the VEGFR2 antagonist ramucirumab in this setting.

The multicenter, double-blind phase 3 RELAY trial accrued 449 patients with stage IV NSCLC harboring an *EGFR* exon 19 deletion or exon 21 L858R mutation who had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Patients were excluded if they had a known *EGFR* T790M mutation, prior *EGFR* TKI or chemotherapy treatment, or brain metastases.

Patient characteristics were well balanced between the study arms. The median patient age was 65 years, and 63% of patients were female. Three-fourths of patients were Asian, and a quarter of patients were white. About 60% of patients in each arm were never-smokers, and half the patients in each arm had an ECOG performance status of 0.

Patients were randomized to erlotinib 150 mg/day plus either placebo ( $n = 225$ ) or ramucirumab ( $n = 224$ ) at 10 mg/kg every 2 weeks. Treatment was administered until disease progression or unacceptable toxicity. The primary end point was PFS. Key secondary end points included safety, overall survival (OS), overall response rate (ORR), and duration of response.

OS data are not yet mature. At the data cutoff, there were 37 OS events in the combination arm and 42 in the control arm, with an HR of 0.832 (95% CI, 0.532-1.303) favoring the ramucirumab group.

Likewise, the data remain immature for PFS2, the time from randomization to progression on an additional systemic anticancer treatment. There were 61 and 79 PFS2 events in the combination and control arms, respectively, with an HR of 0.690 (95% CI, 0.490-0.972) favoring the ramucirumab arm.

The ORRs were 76% with the combination and 75% in the control arm. The disease control rate was 95% versus 96%, respectively. The median duration of response favored the ramucirumab arm at 18.0 months compared with 11.1 months for the erlotinib-alone group.

Seventy percent of patients in the ramucirumab arm and 81% of patients in the erlotinib-alone arm had discontinued treatment at the data cutoff of January 23, 2019. Progressive disease was the primary reason for discontinuation in both arms.

The rate of grade  $\geq 3$  treatment-emergent adverse events (TEAEs) was 72% with the ramucirumab combination

compared with 54% with erlotinib alone. The rates of serious TEAEs were 29% versus 21%, respectively. The rates of TEAE-related treatment discontinuation, dose adjustment, and death in the combination versus control arms were 13% versus 11%, 85% versus 71%, and 1% versus 0%, respectively.

Two patients in the ramucirumab arm and 3 patients in the control arm had grade 4 increased alanine aminotransferase (ALT) levels. One patient receiving erlotinib alone had grade 4 increased aspartate aminotransferase (AST) levels. The most common grade 3 TEAEs in the ramucirumab arm were hypertension (24% vs 5% in the erlotinib-alone arm), acneiform

dermatitis (15% vs 9%, respectively), increased ALT (8% vs 6%), diarrhea (7% vs 1%), and increased AST (5% vs 4%). ♦

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#### REFERENCE

Nakagawa K, Garon EB, Seto T, et al. RELAY: a multinational, double-blind, randomized phase 3 study of erlotinib (ERL) in combination with ramucirumab (RAM) or placebo (PL) in previously untreated patients with epidermal growth factor receptor mutation-positive (*EGFRm*) metastatic non-small cell lung cancer (NSCLC). *J Clin Oncol*. 2019;37(suppl; abstr 9000).

## Isatuximab Triplet Significantly Improves PFS in Myeloma

Jason M. Broderick

**ADDING ISATUXIMAB TO POMALIDOMIDE** (Pomalyst) and low-dose dexamethasone led to a >40% reduction in the risk of disease progression or death compared with pomalidomide and dexamethasone alone (Pd) in patients with relapsed/refractory multiple myeloma, according to findings from the phase 3 ICARIA-MM trial presented at the 2019 American Society of Clinical Oncology Annual Meeting.<sup>1</sup>

At a median follow-up of 11.6 months, the median progression-free survival (PFS) per independent review was 11.53 months with the isatuximab regimen compared with 6.47 months with Pd alone (hazard ratio [HR], 0.596; 95% CI, 0.44-0.81;  $P = .001$ ).

Overall survival (OS) data were not yet mature at the time of analysis, but there was a trend toward a survival benefit for the isatuximab arm (HR, 0.687; 95% CI, 0.461-1.023). The median OS was not reached in either arm. The 1-year OS rate was 72% with the isatuximab triplet compared with 63% with Pd alone.

“Isatuximab in combination with pomalidomide and dexamethasone resulted in an impressive 40% reduction in the risk of progression or death compared [with] pomalidomide and dexamethasone alone,” said principal investigator Paul Richardson, MD, clinical program leader and director of clinical research at the Jerome Lipper Multiple Myeloma Center at Dana-Farber Cancer Institute in Boston, Massachusetts.

“This outcome is noteworthy because this trial included a particularly difficult-to-treat relapsed and refractory patient population that was, in my view, highly reflective of real-world practice,” added Richardson.

The open-label, multicenter phase 3 ICARIA-MM trial included 307 patients with relapsed/refractory multiple myeloma who had received at least 2 prior lines of treatment, including lenalidomide (Revlimid) and a proteasome inhibitor (PI).

Patient characteristics were well balanced between the 2 arms. The median patient age was 67 years (range, 36-86), and patients had received a median of 3 (range, 2-11) prior lines of therapy. Overall, 92.5% of patients were lenalidomide refractory, 75.9% were refractory to PI, and 19.5% had high-risk disease cytogenetics.

In the isatuximab arm, 97.4% of patients were refractory to their last line of therapy compared with 98.7% of patients in the Pd arm. In the isatuximab group, 60.4% of patients were refractory to lenalidomide at their last line compared with 57.5% of patients in the control arm.

Isatuximab was administered intravenously at 10 mg/kg once weekly for 4 weeks followed by biweekly administration for 28-day cycles in combination with standard Pd for the duration of therapy. A total of 154 patients were in the isatuximab arm, and 153 patients were in the control arm of Pd alone. Treatment continued until disease progression or unacceptable toxicity. The primary end point was

PFS. Key secondary end points included overall response rate (ORR) and OS.

The PFS results per investigator assessment were similar to the independent review data. The investigator data showed a median PFS of 11.14 months with the isatuximab triplet compared with 6.54 months for the Pd-alone group (HR, 0.602; 95% CI, 0.444-0.816;  $P = .0009$ ).

The PFS benefit held up across multiple patient subgroups, including patients with high cytogenetic risk (HR, 0.66; 95% CI, 0.33-1.28), patients refractory to lenalidomide (HR, 0.59; 95% CI, 0.43-0.82), patients refractory to lenalidomide at their last previous line (HR, 0.50; 95% CI, 0.34-0.76), patients refractory to a PI (HR, 0.58; 95% CI, 0.41-0.82), and patients refractory to lenalidomide and a PI (HR, 0.58; 95% CI, 0.40-0.84).

The ORR was 60.4% in the isatuximab arm compared with 35.3% in the Pd-alone arm ( $P < .0001$ ). The ORR in the isatuximab group comprised a complete response (CR)/ stringent CR rate of 4.5%, a very good partial response rate of 27.3%, and a partial response rate of 28.6%. The corresponding numbers for the control arm were 2.0%, 6.5%, and 26.8%, respectively.

The median time to first response was 35 days with the isatuximab triplet compared with 58 days with Pd alone. The minimal residual disease negativity rate was 5.2% with isatuximab versus 0% with Pd alone.

The median time to next therapy was not reached in the isatuximab arm compared with 9.1 months in the control arm (HR, 0.538; 95% CI, 0.382-0.758). Sixty patients in the isatuximab group and 83 patients in the Pd-alone group received subsequent antimyeloma therapy. These treatments included alkylating agents (66.7% of patients in the isatuximab arm vs 39.8% of patients in the Pd-alone arm), PIs

(56.7% vs 47.0%, respectively), immunomodulatory drugs (23.3% vs 22.9%), and daratumumab (10.0% vs 54.2%).

The median duration of treatment was 41.0 weeks (range, 1.3-76.7) in the isatuximab arm compared with 24.0 weeks (range, 1.0-73.7) in the control arm. In the isatuximab arm, 56.5% of patients discontinued treatment compared with 74.5% of patients in the Pd-alone arm. Progressive disease was the primary reason for discontinuation in both arms.

Grade  $\geq 3$  treatment-emergent adverse events (TEAEs) occurred in 86.8% of patients in the isatuximab arm compared with 70.5% in the control arm. The rates of serious TEAEs were 61.8% versus 53.7%, respectively.

The rate of TEAE-related discontinuations was 7.2% with the isatuximab triplet compared with 12.8% in the control arm. Deaths related to TEAEs occurred in 7.9% and 9.4% of the 2 arms, respectively.

Grade 4 pneumonia occurred in 1.3% of patients in each arm. The most common grade 3 TEAEs in the isatuximab arm were pneumonia (15.1% vs 13.4% in the Pd-alone arm), fatigue (3.9% vs 0%, respectively), dyspnea (3.9% vs 1.3%), upper respiratory tract infection (3.3% vs 0.7%), asthenia (3.3% vs 2.7%), bronchitis (3.3% vs 0.7%), diarrhea (2.0% vs 0.7%), and back pain (2.0% vs 1.3%). ♦

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#### REFERENCE

Richardson PG, Attal M, S. Rajkumar V, et al. A phase III randomized, open label, multi-center study comparing isatuximab, pomalidomide, and low-dose dexamethasone versus pomalidomide and low-dose dexamethasone in patients with relapsed/refractory multiple myeloma (RRMM). *J Clin Oncol*. 2019;37(suppl; abstr 8004). doi: 10.1200/JCO.2019.37.15\_suppl.8004.

# Treatment Patterns and Outcomes Among Patients With Advanced Cutaneous Squamous Cell Carcinoma in a US Community Oncology Setting

Lynne Lederman, PhD

**RESULTS FROM A RETROSPECTIVE**, observational study presented at the 2019 American Society for Clinical Oncology Annual Meeting offer new insight into treatment patterns and clinical outcomes for patients with advanced cutaneous squamous cell carcinoma (CSCC) in a US community oncology setting.<sup>1</sup> Advanced CSCC includes both locally advanced CSCC (laCSCC) and metastatic CSCC (mCSCC).

C. Lance Cowey, MD, and colleagues used data from The US Oncology Network's iKnowMed electronic health record database and chart review to conduct a retrospective, observational study of adult patients with laCSCC and mCSCC. The patient population included those whose first-line systemic treatment commenced between January 1, 2008, and December 31, 2015.<sup>1</sup>

**[T]he authors suggested that these data provide a benchmark for the outcomes of patients with advanced CSCC prior to the 2018 FDA approval of cemiplimab-rwlc.**

Patients required an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1 for inclusion in the study. Patients could be excluded from the trial if they had tumors of an unknown primary site, were treated with an anti-programmed cell death receptor (PD) 1/anti-PD-ligand 1 agent, participated in a clinical trial, or had a concurrent primary cancer.<sup>1</sup>

A total of 82 patients met the inclusion criteria; 17 patients had laCSCC, and 65 had mCSCC. During the initiation of first-line treatment, the median age was 75

years. Most of the patients were male (85%) and white (79%). Eighty-eight percent of patients had an ECOG PS of 1, 90% had prior surgery, and 84% had prior radiotherapy. Of the patients in the study population, 8.5% had received a prior organ transplant.

The most common first-line regimens in the study population were combination carboplatin plus paclitaxel (27%) and single-agent cetuximab (24%). The median duration of first-line treatment was 2.4 months for the entire study population; the median duration was 4.1 months for patients with laCSCC and 2.3 months for those with mCSCC.

The physician-assessed response rate for first-line treatment was 18.3% for the whole study population. In the laCSCC population, the physician-assessed response rate for first-line treatment was 17.6%; for those with mCSCC, it was 18.5%.

From the initiation of first-line treatment, the median overall survival (OS) for the entire study population was 15.3 months (95% CI, 10.4-21.0). The OS for patients with laCSCC was 16.2 months compared with 15.3 months for those with mCSCC. Only 24 patients (29%) received second-line treatment.

According to the authors, their study is the largest retrospective data set involving patients with advanced CSCC who have been treated with conventional chemotherapy. They concluded that efficacy was low in both the laCSCC and mCSCC patient populations. Moreover, the authors suggested that these data provide a benchmark for the outcomes of patients with advanced CSCC prior to the 2018 FDA approval of cemiplimab-rwlc, a monoclonal antibody that blocks PD-1 and is indicated for patients with mCSCC or laCSCC who are not candidates for curative surgery or curative radiation.<sup>1,2</sup> ♦

## REFERENCES

1. Cowey CL, Robert NH, Davies K, et al. Treatment patterns and outcomes among patients with advanced cutaneous squamous cell carcinoma (CSCC) in a US community oncology setting. *J Clin Oncol*. 2019;37(suppl); abstr e21033. doi: 10.1200/JCO.2019.37.15\_suppl.e21033.
2. Libtayo [prescribing information]. Tarrytown, NY, and Bridgewater, NJ: Regeneron Pharmaceuticals Inc; Sanofi-Aventis US LLC; 2018. libtayohcp.com.

Effective April 1, 2019, the following C-code can be used for administrative and billing purposes specific to LIBTAYO® (cemiplimab-rwlc):



# C9044, INJECTION, cemiplimab-rwlc, 1 mg, for hospital outpatient use

For dates of service prior to **April 1, 2019**, use the appropriate unspecified HCPCS C-code (C9399 for unclassified drugs or biologics) to bill for LIBTAYO.

## How supplied<sup>1</sup>

LIBTAYO is supplied in a carton containing 1 single-dose vial of 350 mg/7 mL (50 mg/mL).

## Recommended dosage<sup>1</sup>

The recommended dosage of LIBTAYO is 350 mg administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression or unacceptable toxicity.

The Centers for Medicare & Medicaid Services assigned a 1 mg billing unit for LIBTAYO (1 mg of LIBTAYO = 1 unit). Coding requirements may vary by payer; please verify coding requirements before submitting claims.

## Indication

LIBTAYO is indicated for the treatment of patients with metastatic cutaneous squamous cell carcinoma (CSCC) or locally advanced CSCC who are not candidates for curative surgery or curative radiation.

## Important Safety Information

### Warnings and Precautions

#### Severe and Fatal Immune-Mediated Adverse Reactions

Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue and usually occur during treatment; however, they can also occur after discontinuation. Early identification and management are essential to ensuring safe use of PD-1–blocking antibodies. Monitor for symptoms and signs of immune-mediated adverse reactions. Evaluate clinical chemistries, including liver tests and thyroid function tests, at baseline and periodically during treatment. Institute medical management promptly to include specialty consultation as appropriate.

In general, withhold LIBTAYO for Grade 3 or 4 and certain Grade 2 immune-mediated adverse reactions. Permanently discontinue LIBTAYO for Grade 4 and certain Grade 3 immune-mediated adverse reactions. For Grade 3 or 4 and certain Grade 2 immune-mediated adverse reactions, administer corticosteroids (1 to 2 mg/kg/day prednisone or equivalent) or other appropriate therapy until improvement to Grade 1 or less followed by a corticosteroid taper over 1 month. Consider administration of other systemic immunosuppressants in patients whose immune-mediated adverse reaction is not controlled with corticosteroids. Institute hormone replacement therapy for endocrinopathies as warranted.

**Please see additional Important Safety Information throughout and accompanying Brief Summary of Prescribing Information on the following pages.**



### Strength<sup>1</sup>

350 mg/7 mL (50 mg/mL)

### NDC<sup>1</sup>

61755-008-01

**Immune-mediated pneumonitis:** Immune-mediated pneumonitis occurred in 2.4% of 534 patients receiving LIBTAYO, including Grade 5 (0.2%), Grade 3 (0.7%), and Grade 2 (1.3%). Pneumonitis led to permanent discontinuation of LIBTAYO in 1.3% of patients. Systemic corticosteroids were required in all patients with pneumonitis, including 85% who received prednisone  $\geq$ 40 mg/day or equivalent. Pneumonitis resolved in 62% of patients. Withhold LIBTAYO for Grade 2, and permanently discontinue for Grade 3 or 4. Resume in patients with complete or partial resolution (Grade 0 to 1) after corticosteroid taper.

**Immune-mediated colitis:** Immune-mediated colitis occurred in 0.9% of 534 patients receiving LIBTAYO, including Grade 3 (0.4%) and Grade 2 (0.6%). Colitis led to permanent discontinuation of LIBTAYO in 0.2% of patients. Systemic corticosteroids were required in all patients with colitis, including 60% who received prednisone  $\geq$ 40 mg/day or equivalent. Colitis resolved in 80% of patients. Withhold LIBTAYO for Grade 2 or 3, and permanently discontinue for Grade 4. Resume in patients with complete or partial resolution (Grade 0 to 1) after corticosteroid taper.

**Immune-mediated hepatitis:** Immune-mediated hepatitis occurred in 2.1% of 534 patients receiving LIBTAYO, including Grade 5 (0.2%), Grade 4 (0.2%), and Grade 3 (1.7%). Hepatitis led to permanent discontinuation of LIBTAYO in 0.9% of patients. Systemic corticosteroids were required in all patients with hepatitis, including 91% who received prednisone  $\geq$ 40 mg/day or equivalent. Hepatitis resolved in 64% of patients. Withhold LIBTAYO if AST or ALT increases to more than 3 and up to 10 times the upper limit of normal (ULN) or if total bilirubin increases up to 3 times the ULN. Permanently discontinue LIBTAYO if AST or ALT increases to more than 10 times the ULN or total bilirubin increases to more than 3 times the ULN. Resume in patients with complete or partial resolution (Grade 0 to 1) after corticosteroid taper.

(Continued)

# Important Safety Information

## Warnings and Precautions (continued)

**Immune-mediated endocrinopathies:** Withhold LIBTAYO if clinically necessary for Grade 2, 3, or 4.

- **Adrenal insufficiency:** Adrenal insufficiency occurred in 0.4% of 534 patients receiving LIBTAYO, including Grade 3 (0.2%) and Grade 2 (0.2%)
- **Hypophysitis:** Hypophysitis, which can result in hypopituitarism, occurred in 0.2% of 534 patients receiving LIBTAYO, which consisted of 1 patient with Grade 3 hypophysitis
- **Hypothyroidism:** Hypothyroidism occurred in 6% of 534 patients receiving LIBTAYO, including Grade 3 (0.2%) and Grade 2 (5.6%); no patients discontinued hormone replacement therapy
- **Hyperthyroidism:** Hyperthyroidism occurred in 1.5% of 534 patients receiving LIBTAYO, including Grade 3 (0.2%) and Grade 2 (0.4%); hyperthyroidism resolved in 38% of patients
- **Type 1 diabetes mellitus:** Type 1 diabetes mellitus, which can present with diabetic ketoacidosis, occurred in 0.7% of 534 patients, including Grade 4 (0.4%) and Grade 3 (0.4%); type 1 diabetes mellitus led to permanent discontinuation of LIBTAYO in 0.2% of patients

**Immune-mediated nephritis with renal dysfunction:** Immune-mediated nephritis occurred in 0.6% of 534 patients receiving LIBTAYO, including Grade 3 (0.4%) and Grade 2 (0.2%). Nephritis led to permanent discontinuation of LIBTAYO in 0.2% of patients. Systemic corticosteroids were required in all patients with nephritis, including 67% who received prednisone  $\geq$ 40 mg/day or equivalent. Nephritis resolved in all patients. Withhold LIBTAYO for Grade 3, and permanently discontinue for Grade 4. Resume in patients with complete or partial resolution (Grade 0 to 1) after corticosteroid taper.

**Immune-mediated dermatologic adverse reactions:** Immune-mediated dermatologic reactions, including erythema multiforme and pemphigoid, occurred in 1.7% of 534 patients receiving LIBTAYO, including Grade 3 (1.1%) and Grade 2 (0.6%). In addition, SJS and TEN have been observed with LIBTAYO and with other products in this class. Systemic corticosteroids were required in all patients with dermatologic reactions, including 89% who received prednisone  $\geq$ 40 mg/day or equivalent. Dermatologic reactions resolved in 33% of patients. Approximately 22% of patients had recurrence of dermatologic reactions after re-initiation of LIBTAYO. Withhold LIBTAYO for Grade 3, and permanently discontinue for Grade 4. Resume in patients with complete or partial resolution (Grade 0 to 1) after corticosteroid taper.

**Other immune-mediated adverse reactions:** The following clinically significant immune-mediated adverse reactions occurred at an incidence of  $<$ 1% in 534 patients who received LIBTAYO or were reported with the use of other PD-1–blocking and PD-L1–blocking antibodies. Severe or fatal cases have been reported for some of these adverse reactions. Withhold LIBTAYO for Grade 3, and permanently discontinue for Grade 4. Resume in patients with complete or partial resolution (Grade 0 to 1) after corticosteroid taper.

- **Neurological:** Meningitis, encephalitis, myelitis and demyelination, myasthenic syndrome/myasthenia gravis, Guillain-Barré syndrome, nerve paresis, and autoimmune neuropathy
- **Cardiovascular:** Myocarditis, pericarditis, and vasculitides
- **Ocular:** Uveitis, iritis, and other ocular inflammatory toxicities. Some cases can be associated with retinal detachment. Various grades of visual impairment to include blindness can occur. If uveitis occurs in combination with other immune-mediated adverse reactions, consider a Vogt-Koyanagi-Harada–like syndrome, as this may require treatment with systemic corticosteroids to reduce the risk of permanent vision loss

- **Gastrointestinal:** Pancreatitis to include increases in serum amylase and lipase levels, gastritis, and duodenitis
- **Musculoskeletal and connective tissue:** Myositis, rhabdomyolysis, and associated sequelae, including renal failure, arthritis, and polymyalgia rheumatica
- **Hematological and immunological:** Hemolytic anemia, aplastic anemia, hemophagocytic lymphohistiocytosis, systemic inflammatory response syndrome, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immune thrombocytopenic purpura, and solid organ transplant rejection

## Infusion-related reactions

Severe infusion-related reactions (Grade 3) occurred in 0.2% of patients receiving LIBTAYO. Monitor patients for signs and symptoms of infusion-related reactions. Interrupt or slow the rate of infusion for Grade 1 or 2, and permanently discontinue for Grade 3 or 4.

## Embryo-fetal toxicity

LIBTAYO can cause fetal harm when administered to a pregnant woman due to an increased risk of immune-mediated rejection of the developing fetus resulting in fetal death. Advise women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with LIBTAYO and for at least 4 months after the last dose.

## Adverse reactions

- Serious adverse reactions occurred in 28% of patients. Serious adverse reactions that occurred in  $\geq$ 2% of patients were cellulitis, sepsis, pneumonia, pneumonitis, and urinary tract infection. The most common Grade 3–4 adverse reactions ( $\geq$ 2%) were cellulitis, sepsis, hypertension, pneumonia, musculoskeletal pain, skin infection, urinary tract infection, and fatigue
- LIBTAYO was permanently discontinued due to adverse reactions in 5% of patients; adverse reactions resulting in permanent discontinuation were pneumonitis, autoimmune myocarditis, hepatitis, aseptic meningitis, complex regional pain syndrome, cough, and muscular weakness
- The most common adverse reactions (incidence  $\geq$ 20%) were fatigue, rash, and diarrhea

## Use in specific populations

- **Lactation:** Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment and for at least 4 months after the last dose of LIBTAYO
- **Females and males of reproductive potential:** Verify pregnancy status in females of reproductive potential prior to initiating LIBTAYO

## Please see accompanying Brief Summary of Prescribing Information on the following pages.

**Reference:** LIBTAYO (cemiplimab-rwlc) injection full U.S. prescribing information. Regeneron Pharmaceuticals, Inc., and sanofi-aventis U.S. LLC.

ALT=alanine aminotransferase; AST=aspartate aminotransferase; PD-1=programmed death receptor-1; NDC=National Drug Code.



**LIBTAYO® (cemiplimab-rwlc) injections, for intravenous use**  
Brief Summary of Prescribing Information

## 1 INDICATIONS AND USAGE

LIBTAYO is indicated for the treatment of patients with metastatic cutaneous squamous cell carcinoma (CSCC) or locally advanced CSCC who are not candidates for curative surgery or curative radiation.

## 2 DOSAGE AND ADMINISTRATION

### 2.1 Recommended Dosage

The recommended dosage of LIBTAYO is 350 mg administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression or unacceptable toxicity.

### 2.2 Dosage Modifications for Adverse Reactions

Withhold or discontinue LIBTAYO to manage adverse reactions as described in Table 1. No dose reduction of LIBTAYO is recommended.

**Table 1: Recommended Dosage Modifications for Adverse Reactions**

Adverse Reaction	Severity*	LIBTAYO Dosage Modifications
<b>Severe and Fatal Immune-Mediated Adverse Reactions [see Warnings and Precautions (5.1)]</b>		
Pneumonitis	Grade 2	Withhold†
	Grades 3 or 4	Permanently discontinue
Colitis	Grades 2 or 3	Withhold†
	Grade 4	Permanently discontinue
Hepatitis	If AST or ALT increases to more than 3 and up to 10 times the upper limit of normal (ULN) or if total bilirubin increases up to 3 times the ULN.	Withhold†
	If AST or ALT increases to more than 10 times the ULN or total bilirubin increases to more than 3 times the ULN	Permanently discontinue
Endocrinopathies	Grades 2, 3, or 4	Withhold if clinically necessary
Other immune-mediated adverse reactions involving a major organ	Grade 3	Withhold†
	Grade 4	Permanently discontinue
Recurrent or persistent immune mediated adverse reactions	<ul style="list-style-type: none"> <li>Recurrent Grade 3 or 4</li> <li>Grade 2 or 3 persistent for 12 weeks or longer after last LIBTAYO dose</li> <li>Requirement for 10 mg per day or greater prednisone or equivalent lasting 12 weeks or longer after last LIBTAYO dose</li> </ul>	Permanently discontinue
<b>Other Adverse Reactions</b>		
Infusion-related reactions [see Warnings and Precautions (5.2)]	Grade 1 or 2	Interrupt or slow the rate of infusion
	Grade 3 or 4	Permanently discontinue

\*Toxicity graded per National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0

†Resume in patients with complete or partial resolution (Grade 0 to 1) after corticosteroid taper.

### 2.3 Preparation and Administration

- Visually inspect for particulate matter and discoloration prior to administration. LIBTAYO is a clear to slightly opalescent, colorless to pale yellow solution that may contain trace amounts of translucent to white particles. Discard the vial if the solution is cloudy, discolored or contains extraneous particulate matter other than trace amounts of translucent to white particles.

#### Preparation

- Do not shake.
- Withdraw 7 mL from a vial and dilute with 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to a final concentration between 1 mg/mL to 20 mg/mL.
- Mix diluted solution by gentle inversion. Do not shake.
- Discard any unused medicinal product or waste material.

#### Storage and Infusion Solution

- Store at room temperature up to 25°C (77°F) for no more than 8 hours from the time of preparation to the end of the infusion or at 2°C to 8°C (36°F to 46°F) for no more than 24 hours from the time of preparation to the end of infusion.
- Allow the diluted solution to come to room temperature prior to administration.
- Do not freeze.

#### Administration

- Administer by intravenous infusion over 30 minutes through an intravenous line containing a sterile, in-line or add-on 0.2-micron to 5-micron filter.

## 4 CONTRAINDICATIONS

None.

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Severe and Fatal Immune-Mediated Adverse Reactions

LIBTAYO is a monoclonal antibody that belongs to a class of drugs that binds to the programmed death receptor-1 (PD-1), blocking the PD-1/PD-L1 pathway, thereby removing inhibition of the immune response with the potential for breaking of peripheral tolerance and induction of immune-mediated adverse reactions. Important immune-mediated adverse reactions listed under Warnings and Precautions may not be inclusive of all possible immune-mediated reactions.

Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue. While immune-mediated adverse reactions usually manifest during treatment with PD-1/PD-L1 blocking antibodies, immune-mediated adverse reactions can also manifest after discontinuation of PD-1/PD-L1 blocking antibodies.

Early identification and management are essential to ensure safe use of PD-1/PD-L1 blocking antibodies. Monitor for symptoms and signs of immune-mediated adverse reactions. Evaluate clinical chemistries, including liver tests and thyroid function tests, at baseline and periodically during treatment. Institute medical management promptly to include specialty consultation as appropriate.

In general, withhold LIBTAYO for Grade 3 or 4 and certain Grade 2 immune-mediated adverse reactions. Permanently discontinue LIBTAYO for Grade 4 and certain Grade 3 immune-mediated adverse reactions [see Dosage and Administration (2.2)]. For Grade 3 or 4 and certain Grade 2 immune-mediated adverse reactions, administer corticosteroids (1 to 2 mg/kg/day prednisone or equivalent) or other appropriate therapy until improvement to Grade 1 or less followed by a corticosteroid taper over one month [see Dosage and Administration (2.2)]. Consider administration of other systemic immunosuppressants in patients whose immune-mediated adverse reaction is not controlled with corticosteroids. Institute hormone replacement therapy for endocrinopathies as warranted.

#### Immune-Mediated Pneumonitis

Immune-mediated pneumonitis occurred in 2.4% of 534 patients receiving LIBTAYO, including Grade 5 (0.2%), Grade 3 (0.7%) and Grade 2 (1.3%) [see Adverse Reactions (6.1)]. Pneumonitis led to permanent discontinuation of LIBTAYO in 1.3% of patients. Systemic corticosteroids were required in all patients with pneumonitis, including 85% who received prednisone ≥40 mg per day or equivalent. Pneumonitis resolved in 62% of patients.

#### Immune-Mediated Colitis

Immune-mediated colitis occurred in 0.9% of 534 patients receiving LIBTAYO, including Grade 3 (0.4%) and Grade 2 (0.6%) [see Adverse Reactions (6.1)]. Colitis led to permanent discontinuation of LIBTAYO in 0.2% of patients. Systemic corticosteroids were required in all patients with colitis, including 60% who received prednisone ≥40 mg per day or equivalent. Colitis resolved in 80% of patients.

#### Immune-Mediated Hepatitis

Immune-mediated hepatitis occurred in 2.1% of 534 patients receiving LIBTAYO, including Grade 5 (0.2%), Grade 4 (0.2%), and Grade 3 (1.7%) [see Adverse Reactions (6.1)]. Hepatitis led to permanent discontinuation of LIBTAYO in 0.9% of patients. Systemic corticosteroids were required in all patients with hepatitis, including 91% who received prednisone ≥40 mg per day or equivalent. Hepatitis resolved in 64% of patients.

#### Immune-Mediated Endocrinopathies

##### Adrenal Insufficiency

Adrenal insufficiency occurred in 0.4% of 534 patients receiving LIBTAYO, including Grade 3 (0.2%), and Grade 2 (0.2%) [see Adverse Reactions (6.1)].

##### Hypophysitis

Hypophysitis, which can result in hypopituitarism, occurred in 0.2% of 534 patients receiving LIBTAYO, which consisted of one patient with Grade 3 hypophysitis.

##### Hypothyroidism

Hypothyroidism occurred in 6% of 534 patients receiving LIBTAYO, including Grade 3 (0.2%) and Grade 2 (5.6%). No patients discontinued hormone replacement therapy.

##### Hyperthyroidism

Hyperthyroidism occurred in 1.5% of 534 patients receiving LIBTAYO, including Grade 3 (0.2%) and Grade 2 (0.4%). Hyperthyroidism resolved in 38% of patients.

##### Type 1 Diabetes Mellitus

Type 1 diabetes mellitus, which can present with diabetic ketoacidosis, occurred in 0.7% of 534 patients, including Grade 4 (0.4%) and Grade 3 (0.4%). Type 1 diabetes mellitus led to permanent discontinuation of LIBTAYO in 0.2% of patients.

#### Immune-Mediated Nephritis with Renal Dysfunction

Immune-mediated nephritis occurred in 0.6% of 534 patients receiving LIBTAYO, including Grade 3 (0.4%) and Grade 2 (0.2%) [see Adverse Reactions (6.1)]. Nephritis led to permanent discontinuation of LIBTAYO in 0.2% of patients. Systemic corticosteroids were required in all patients with nephritis, including 67% who received prednisone ≥40 mg per day or equivalent. Nephritis resolved in all patients.

#### Immune-Mediated Dermatologic Adverse Reactions

Immune-mediated dermatologic reactions, including erythema multiforme and pemphigoid, occurred in 1.7% of 534 patients receiving LIBTAYO, including Grade 3 (1.1%) and Grade 2 (0.6%) [see Adverse Reactions (6.1)]. In addition, SJS and TEN have been observed with LIBTAYO and with other products in this class. Systemic corticosteroids were required in all patients with dermatologic reactions, including 89% who received prednisone ≥40 mg per day or equivalent. Dermatologic reactions resolved in 33% of patients. Approximately 22% of patients had recurrence of dermatologic reactions after re-initiation of LIBTAYO.

#### Other Immune-Mediated Adverse Reactions

The following clinically significant immune-mediated adverse reactions occurred at an incidence of <1% in 534 patients who received LIBTAYO [see Adverse Reactions (6.1)] or were reported with the use of other PD-1/PD-L1 blocking antibodies. Severe or fatal cases have been reported for some of these adverse reactions.

**Neurological:** Meningitis, encephalitis, myelitis and demyelination, myasthenic syndrome / myasthenia gravis, Guillain-Barre syndrome, nerve paresthesia, autoimmune neuropathy

**Cardiovascular:** Myocarditis, pericarditis, vasculitides

**Ocular:** Uveitis, iritis, and other ocular inflammatory toxicities. Some cases can be associated with retinal detachment. Various grades of visual impairment to include blindness can occur. If uveitis occurs in combination with other immune-mediated adverse reactions, consider a Vogt-Koyanagi-Harada like syndrome, as this may require treatment with systemic corticosteroids to reduce the risk of permanent vision loss.

**Gastrointestinal:** Pancreatitis to include increases in serum amylase and lipase levels, gastritis, duodenitis

**Musculoskeletal and Connective Tissue:** Myositis, rhabdomyolysis and associated sequelae including renal failure, arthritis, polymyalgia rheumatica

**Hematological and Immunological:** Hemolytic anemia, aplastic anemia, hemophagocytic lymphohistiocytosis, systemic inflammatory response syndrome, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immune thrombocytopenic purpura, solid organ transplant rejection.

### 5.2 Infusion-Related Reactions

Severe infusion-related reactions (Grade 3) occurred in 0.2% of patients receiving LIBTAYO [see *Adverse Reactions (6.1)*]. Monitor patients for signs and symptoms of infusion-related reactions. Interrupt or slow the rate of infusion or permanently discontinue LIBTAYO based on severity of reaction [see *Dosage and Administration (2.2)*].

### 5.3 Embryo-Fetal Toxicity

Based on its mechanism of action, LIBTAYO can cause fetal harm when administered to a pregnant woman. Animal studies have demonstrated that inhibition of the PD-1/PD-L1 pathway can lead to increased risk of immune-mediated rejection of the developing fetus resulting in fetal death. Advise women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with LIBTAYO and for at least 4 months after the last dose [see *Use in Specific Populations (8.1, 8.3)*].

## 6 ADVERSE REACTIONS

The following serious adverse reactions are described elsewhere in the labeling.

- Severe and Fatal Immune-Mediated Adverse Reactions [see *Warnings and Precautions (5.1)*]
- Infusion-Related Reactions [see *Warnings and Precautions (5.2)*]

### 6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data described in WARNINGS AND PRECAUTIONS reflect exposure to LIBTAYO in 534 patients in two open-label, single-arm, multicohort studies (Study 1423 and Study 1540), including 98 patients with metastatic (nodal or distant) CSCC, 65 patients with locally advanced CSCC, and 371 patients with other advanced solid tumors. LIBTAYO as a single agent or in combination with chemotherapy or radiation was administered intravenously at doses of 1 mg/kg every 2 weeks (n=27), 3 mg/kg every 2 weeks (n=446), 3 mg/kg every 3 weeks (n=12), 10 mg/kg every 2 weeks (n=6), 200 mg every 2 weeks (n=20) or 350 mg every 3 weeks (n=23). Among the 534 patients, 38% were exposed for ≥6 months and 16% were exposed for ≥12 months.

The data described below reflect exposure to LIBTAYO in 163 patients with advanced CSCC (metastatic or locally advanced disease) in Study 1423 and Study 1540. Patients received LIBTAYO 1 mg/kg every 2 weeks (n=1), 3 mg/kg every 2 weeks (n=139) or 350 mg every 3 weeks (n=23) as an intravenous infusion until disease progression, unacceptable toxicity, or completion of planned treatment. The median duration of exposure was 20 weeks (3 days to 1.4 years).

The safety population characteristics were: median age of 71 years (38 to 96 years), 85% male, 96% white, and ECOG performance score (PS) of 0 (44%) or 1 (56%).

The most common adverse reactions reported in at least 20% of patients were fatigue, rash and diarrhea. The most common Grade 3-4 adverse reactions (≥2%) were cellulitis, sepsis, hypertension, pneumonia, musculoskeletal pain, skin infection, urinary tract infection and fatigue. LIBTAYO was permanently discontinued due to adverse reactions in 5% of patients; adverse reactions resulting in permanent discontinuation were pneumonitis, autoimmune myocarditis, hepatitis, aseptic meningitis, complex regional pain syndrome, cough, and muscular weakness. Serious adverse reactions occurred in 28% of patients. Serious adverse reactions that occurred in at least 2% of patients were cellulitis, sepsis, pneumonia, pneumonitis and urinary tract infection.

Table 2 summarizes the adverse reactions that occurred in ≥10% of patients and Table 3 summarizes Grade 3 and 4 laboratory abnormalities worsening from baseline in ≥1% of patients receiving LIBTAYO.

**Table 2: Adverse Reactions in ≥10% of Patients with Advanced CSCC Receiving LIBTAYO in Study 1423 and Study 1540**

Adverse Reactions	LIBTAYO N=163	
	All Grades %	Grade 3-4 %
<b>Skin and Subcutaneous Tissue</b>		
Rash*	25	1.2
Pruritus†	15	0
<b>Gastrointestinal</b>		
Diarrhea‡	22	0.6
Nausea	19	0
Constipation	12	0.6
<b>General and Administration Site</b>		
Fatigue§	29	2
<b>Musculoskeletal and Connective Tissue</b>		
Musculoskeletal pain¶	17	3
<b>Metabolism and Nutrition</b>		
Decreased appetite	10	0

\*Rash is a composite term that includes rash maculopapular, rash, dermatitis, rash generalized, dermatitis bullous, drug eruption, erythema, rash erythematous, rash macular, rash pruritic, and skin reaction.

†Pruritus is a composite term that includes pruritus and pruritus allergic.

‡Diarrhea is a composite term that includes diarrhea and colitis.

§Fatigue is a composite term that includes fatigue and asthenia.

¶Musculoskeletal pain is a composite term that includes: musculoskeletal pain, back pain, myalgia, neck pain, pain in extremity.

**Table 3: Grade 3 or 4 Laboratory Abnormalities Worsening from Baseline in ≥1% of Patients with Advanced CSCC Receiving LIBTAYO in Study 1423 and Study 1540**

Laboratory Abnormality	Grade 3-4 (%)†
<b>Chemistry</b>	
Increased aspartate aminotransferase	3
Increased INR	2
Hypoalbuminemia	1
<b>Hematology</b>	
Lymphopenia	7
Anemia	2
<b>Electrolytes</b>	
Hypophosphatemia	4
Hyponatremia	3
Hypercalcemia	1

†Percentages are based on the number of patients with at least 1 post-baseline value available for that parameter.

### 6.2 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to cemiplimab-rwlc in the studies described below with the incidence of antibodies in other studies or to other products may be misleading. Anti-drug antibodies (ADA) were tested in 398 of 534 patients who received LIBTAYO and the incidence of cemiplimab-rwlc treatment-emergent ADAs was 1.3% using an electrochemiluminescent (ECL) bridging immunoassay; 0.3% were persistent ADA responses. In the patients who developed anti-cemiplimab-rwlc antibodies, there was no evidence of an altered pharmacokinetic profile of cemiplimab-rwlc.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

#### Risk Summary

Based on its mechanism of action, LIBTAYO can cause fetal harm when administered to a pregnant woman. There are no available data on the use of LIBTAYO in pregnant women. Animal studies have demonstrated that inhibition of the PD-1/PD-L1 pathway can lead to increased risk of immune-mediated rejection of the developing fetus resulting in fetal death (see *Data*). Human IgG4 immunoglobulins (IgG4) are known to cross the placenta; therefore, LIBTAYO has the potential to be transmitted from the mother to the developing fetus. Advise women of the potential risk to a fetus.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

#### Data

##### Animal Data

Animal reproduction studies have not been conducted with LIBTAYO to evaluate its effect on reproduction and fetal development. A central function of the PD-1/PD-L1 pathway is to preserve pregnancy by maintaining maternal immune tolerance to the fetus. In murine models of pregnancy, blockade of PD-L1 signaling has been shown to disrupt tolerance to the fetus and to result in an increase in fetal loss; therefore, potential risks of administering LIBTAYO during pregnancy include increased rates of abortion or stillbirth. As reported in the literature, there were no malformations related to the blockade of PD-1/PD-L1 signaling in the offspring of these animals; however, immune-mediated disorders occurred in PD-1 and PD-L1 knockout mice. Based on its mechanism of action, fetal exposure to cemiplimab-rwlc may increase the risk of developing immune-mediated disorders or altering the normal immune response.

### 8.2 Lactation

#### Risk Summary

There is no information regarding the presence of cemiplimab-rwlc in human milk, or its effects on the breastfed child or on milk production. Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment and for at least 4 months after the last dose of LIBTAYO.

### 8.3 Females and Males of Reproductive Potential

#### Pregnancy Testing

Verify pregnancy status in females of reproductive potential prior to initiating LIBTAYO [see *Use in Specific Populations (8.1)*].

#### Contraception

LIBTAYO can cause fetal harm when administered to a pregnant woman [see *Use in Specific Populations (8.1)*].

##### Females

Advise females of reproductive potential to use effective contraception during treatment with LIBTAYO and for at least 4 months after the last dose.

### 8.4 Pediatric Use

The safety and effectiveness of LIBTAYO have not been established in pediatric patients.

### 8.5 Geriatric Use

Of the 163 patients with metastatic and locally advanced CSCC who received LIBTAYO in clinical studies, 72% were 65 years or older and 37% were 75 years or older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects.

## 17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

#### Immune-Mediated Adverse Reactions

Advise patients that LIBTAYO can cause immune-mediated adverse reactions including the following [see *Warnings and Precautions (5.1)*]:

- Pneumonitis: Advise patients to contact their healthcare provider immediately for signs or symptoms of pneumonitis, including new or worsening symptoms of cough, chest pain, or shortness of breath.
- Colitis: Advise patients to contact their healthcare provider immediately for signs or symptoms of colitis, including diarrhea, blood or mucus in stools, or severe abdominal pain.
- Hepatitis: Advise patients to contact their healthcare provider immediately for signs or symptoms of hepatitis.
- Endocrinopathies: Advise patients to contact their healthcare provider immediately for signs or symptoms of hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, or type 1 diabetes mellitus.
- Nephritis: Advise patients to contact their healthcare provider immediately for signs or symptoms of nephritis.
- Dermatologic Adverse Reactions: Advise patients to contact their healthcare provider immediately if they develop a new rash.

#### Infusion-Related Reactions

Advise patients to contact their healthcare provider immediately for signs or symptoms of infusion-related reactions [see *Warnings and Precautions (5.2)*].

#### Embryo-Fetal Toxicity

Advise females of reproductive potential that LIBTAYO can cause harm to a fetus and to inform their healthcare provider of a known or suspected pregnancy [see *Warnings and Precautions (5.3)* and *Use in Specific Populations (8.1, 8.3)*].

Advise females of reproductive potential to use effective contraception during treatment and for at least 4 months after the last dose of LIBTAYO [see *Use in Specific Populations (8.3)*].

#### Lactation

Advise female patients not to breastfeed while taking LIBTAYO and for at least 4 months after the last dose [see *Use in Specific Populations (8.2)*].

