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Cemiplimab Impresses in a Phase 3 Trial of Cervical Cancer, Regulatory Submission Expected

March 15, 2021

Audrey Sternberg

Promising overall survival results lead to an early stop to a phase 3 trial of cemiplimab versus chemotherapy in relapsed/refractory cervical cancer, according to the drug's developer.

A phase 3 trial of cemiplimab (Libtayo) versus chemotherapy in patients with previously treated metastatic cervical cancer was stopped early based on positive results demonstrating overall survival (OS) superiority of the experimental regimen, according to Sanofi and Regeneron who are responsible for developing the PD-1 inhibitor.

Treatment with cemiplimab (n = 304) reduce the risk of death by 31% compared with chemotherapy (n = 304), with a median OS of 12.0 months versus 8.5 months, respectively (HR, 0.69; 95% CI, 0.56-0.84; P <.0001).

"Libtayo monotherapy is the first medicine to demonstrate an improvement in overall survival in women with recurrent or metastatic cervical cancer following progression on platinum-based chemotherapy in a phase 3 trial," Krishnansu S. Tewari, MD, professor and director of the Division of Gynecologic Oncology at the University of California, Irvine and a trial investigator, said in a press release.

Breaking down the patient population by histology, those with squamous cell carcinoma saw a 27% reduction in the risk of death when treated with cemiplimab, with a median OS of 11.1 months versus 8.8 months with chemotherapy (HR, 0.73; 95% CI, 0.58-0.91; P = .003). In those with adenocarcinoma, the median OS for cemiplimab and chemotherapy were 13.3 months and 7.0 months, respectively, equating to a 44% reduction in the risk of death (HR, 0.56; 95% CI, 0.36-0.85; P <.005).

No new safety signals with cemiplimab were noted. The safety population was comprised of 300 patients receiving cemiplimab and 290 on chemotherapy, with median treatment exposure lasting 15 weeks (range, 1-101) and 10 weeks (range, 1-82), respectively. Adverse events (AEs) were observed in 88% of patients in the cemiplimab group and 91% on chemotherapy; serious AEs were noted in 30% and 27%, respectively. Most common AEs include anemia (25% vs 45%, respectively), nausea (18% vs 33%), fatigue (17% vs 16%), vomiting (16% vs 23%), and constipation (15% vs 20%). Discontinuations as a result of AEs occurred in 8% of the cemiplimab group and 5% of the chemotherapy group.

Patients treated on the trial had recurrent or metastatic cervical cancer that had progressed on platinum-based chemotherapy. The patient population was comprised of 78% squamous cell carcinoma and 22% adenocarcinoma, and the median patient age was 51 years. OS was the primary end point of the trial, analyzed first in the squamous cell population.

Patients receiving cemiplimab monotherapy had treatment at a dose of 350 mg every 3 weeks and those receiving chemotherapy had investigator's choice of either pemetrexed, vinorelbine, topotecan, irinotecan, or gemcitabine.

The trial, which enrolled patients regardless of their PD-L1 status, demonstrated that Libtayo helped patients with recurrent or metastatic cervical cancer live longer after progression on prior chemotherapy. This decision was aided by a unanimous recommendation from the Independent Data Monitoring Committee (IDMC). These data will serve as the basis for regulatory submission of a cervical cancer indication for cemiplimab in 2021.

Reference:

Phase 3 trial of Libtayo (cemiplimab) monotherapy in advanced cervical cancer stopped early for positive result on overall survival. News release. Sanofi and Regenergon. March 15, 2021. Accessed March 15, 2021. https://bit.ly/3tmLCnG

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Cemiplimab Receives Priority Review From the FDA In Recurrent of Metastatic Cervical Cancer

October 4, 2021

Ariana Pelosci

Patients with recurrent or metastatic cervical cancer treated with cemiplimab experienced an improved overall survival, progression-free survival, and overall response rate, leading to priority review from the FDA.

Cemiplimab-rwlc (Libtayo) was granted priority review by the FDA for patients with recurrent or metastatic cervical cancer who have experienced disease progression on or after chemotherapy, according to a press release from Regeneron Pharmaceuticals.1

The clinical decision was based on results of the phase 3 EMPOWER-Cervical 1 trial (NCT03257267). Findings from the overall population highlighted a 31% reduction in the risk of death (HR, 0.69; 95% CI, 0.56-0.84; one-sided P =.00011), as well as a 25% reduction in disease progression (HR, 0.75; 95% CI, 0.63-0.89; one-sided P =.00048) and an overall response rate (ORR) of 16% (n = 50; 95% CI, 13%-21%; one-sided P = .00004). Comparatively, the chemotherapy cohort had an ORR of 6% (n = 19). Patients in the cemiplimab group had a median duration of response of 16 months (95% CI, 12–not yet evaluable) compared with 7 months (95% CI, 5-8) in the chemotherapy group. A total of 78% of patients had squamous cell carcinoma, 239 of whom were in the cemiplimab group and 238 in the chemotherapy group. These patients notably experienced a 27% reduction in risk of death (HR, 0.73; 95% CI, 0.58-0.91; one-sided P =.00306) and a 29% reduction in disease progression (HR, 0.71; 95% CI, 0.58-0.86; one-sided P =.00026). Additionally, the experimental group achieved an ORR of 18% (n =42; 95% CI, 13%-23%) compared with 7% (n = 16) in the chemotherapy group (95% CI, 4%-11%).

The FDA set a target action date of January 31, 2022.

Patients who were treated with the cemiplimab monotherapy or investigator’s choice chemotherapy and were enrolled regardless of tumor PD-L1 expression or histology. The end points of the trial was overall survival (OS), which was assessed in patients with squamous cell carcinoma histology, as well as in the total population.

A total of 304 patients were enrolled in the cemiplimab and 304 patients enrolled in the chemotherapy group. Additional findings from the study indicated that patients in the cemiplimab arm were generally able to improve or maintain their baseline Global Health Status/Quality of Life over time compared with those who were treated with chemotherapy, who experienced clinically meaningful deterioration starting at cycle 8 (P =.00040).

A post-hoc analysis showed that, although assessment of adenocarcinoma was not a prespecified end point, 65 patients treated with cemiplimab and 66 treated with chemotherapy had a 44% reduction in the risk of death (HR, 0.56; 95% CI, 0.36-0.85; nominal one-sided P <.005), as well as a 9% reduction in disease progression (HR, 0.91; 95% CI, 0.62-1.34). Additionally, investigators reported an ORR of 12% (n = 8; 95% CI, 6%-23%) compared with 5% (n = 3; 95% CI, 1%-13%) in the chemotherapy group.

Patients did not experience any new safety signals. Patients who received at least 1 dose of treatment were assessed, including 300 patients in the cemiplimab group and 290 in the chemotherapy group. In 88% of patients in the cemiplimab group and 91% in the chemotherapy group experienced adverse effects (AEs). Some of the most common grade 3 or higher AEs in the cemiplimab and chemotherapy groups, respectively, were asthenia (2% vs 1%) and pyrexia (less than 1% vs, 0%). Patients also experienced immune-related AEs, including 16% of those receiving cemiplimab and less than 1% of those in the chemotherapy group. Additionally, 6% of immune-related AEs were grade 3 or higher in the cemiplimab group, as well as less than 1% in the chemotherapy group. Eight percent of patients in the cemiplimab group and 5% in the chemotherapy group experienced AEs that led to discontinuation.

References

FDA accepts Libtayo (cemiplimab-rwlc) for priority review for advanced cervical cancer. News Release. Regeneron Pharmaceuticals, Inc. September 28, 2021. Accessed October 4, 2021. https://prn.to/3osRTPv

Positive phase 3 Libtayo (cempilimab) results in advanced cervical cancer presented at ESMO Virtual Plenary. News Release. Rengeneron Pharmaceuticals, Inc and Sanofi. May 12, 2021. Accessed October 4, 2021. https://bi

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Second-Line Balstilimab Plus Zalifrelimab Yields Durable Clinical Activity in Recurrent/Metastatic Cervical Cancer

January 7, 2022

Matthew Fowler

Findings from a phase 2 study demonstrated encouraging clinical activity and a manageable safety profile when patients with advanced cervical cancer were treated with second-line balstilimab and zalifrelimab.

The second-line combination of anti–PD-1 agent, balstilimab, and CTLA-4 agent, zalifrelimab (AGEN1884), produced durable clinical activity while maintaining a tolerable safety profile when treating patients with recurrent and/or metastatic cervical cancer who relapsed after a prior platinum-based therapy, according to results from a phase 2 study (NCT03495882) published in the Journal of Clinical Oncology.1

With a median follow-up of 21 months, the confirmed objective response rate (ORR) for patients treated with the combination was 25.6% (95% CI, 18.8%-33.9%), including 10 complete responses and 22 partial responses. “This data suggests the combination of balstilimab and zalifrelimab is an effective and durable new option for treating advanced or recurrent cervical cancers — particularly in patients whose tumors express PD-L1. 2” corresponding author David O’Malley, MD, a gynecologic oncologist at Ohio State University Comprehensive Cancer Center

Patient enrollment occurred from August 27, 2018, to May 7, 2020, at 45 sites in the United States, Europe, South America, and Australia. Patient eligibility required confirmed diagnosis of recurrent and/or metastatic squamous cell carcinoma, adenosquamous carcinoma, or adenocarcinoma of the cervix in order enroll. Additional requirements included being 18 years of age or older, having an ECOG performance

status of 0 or 1, and having adequate hematologic, renal, and hepatic function. Patients also had to have at least 1 measurable lesion by RECIST 1.1 and relapsed following treatment with a first-line, platinum-based therapy.

In terms of dosing, balstilimab was administered intravenously at 3 mg/kg once every 2 weeks plus 1 mg/kg zalifrelimab intravenously once every 6 weeks during a 6-week cycle. Treatment continued until disease progression, unacceptable toxicities, or investigator and/or patient decision.The primary end point was ORR assessed by independent review committee. Secondary end points included duration of response (DOR), disease control rate (DCR), duration of stable disease, safety and tolerability, and survival.A total of 155 patients were enrolled on the study and received treatment with balstilimab and zalifrelimab. Patients had a median age of 50 years (range, 24-76). The majority of patients were White (95.5%), had squamous cell carcinoma (70.3%), and previously received radiotherapy (89%). Most patients also had an ECOG performance status of 0 (57.4%) and PD-L1–positive tumors (55.5%).The median DOR was not reached (NR) for the population of patients (95% CI, 9.7-NR), the median time to response was 2.7 months (95% CI, 1.3-15.8), and the DCR was 52% (95% CI, 43.3%-60.6%). The median progression-free survival (PFS) was 2.7 months (95% CI, 1.5-3.7) and the 12-month PFS rate was 21.3% (95% CI, 14.1%-29.4%). The median overall survival (OS) was 12.8 months (95% CI, 8.8-17.6). The 6-month OS rate was 69.2% (95% CI, 60.1%-76.7%) and the 12-month OS rate was 53.3% (95% CI, 43.8%-61.9%).The subset analyses yielded an ORR of 32.8% (95% CI, 22.8%-44.7%) among patients with PD-L1–positive tumors and 9.1% for PD-L1–negative tumors.Common any-grade treatment-related adverse effects (TRAEs) for the overall cohort included hypothyroidism (16.8%), diarrhea (14.2%), fatigue (11.6%), and nausea (9.0%). Grade 3 or higher TRAEs were observed in 20.0% of patients, with commonly reported TRAEs including alanine transaminase increase (2.6%) and diarrhea (1.9%).

References

1. O'Malley DM, Neffa M, Monk BJ, et al. Dual PD-1 and CTLA-4 checkpoint blockade using balstilimab and zalifrelimab combination as second-line treatment for advanced cervical cancer: an open-label phase II study. J Clin Oncol. Published online December 21, 2021. doi:10.1200/JCO.21.02067

2. Targeted two-drug therapy effective to treat advanced cervical cancer. News release. Ohio State University Comprehensive Cancer Center. January 4, 2022. Accessed January 5, 2022. https://tinyurl.com/5exmde2b

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FDA Grants Accelerated Approval to Tisotumab Vedotin in Recurrent Or Metastatic Cervical Cancer

September 20, 2021

Audrey Sternberg

Tisotumab vedotin may now be used to treat patients with recurrent or metastatic cervical cancer after the FDA's decision to grant the agent an accelerated approval.

Accelerated approval has been granted to tisotumab vedotin-tftv (Tivdak) for the treatment of patients with recurrent or metastatic cervical cancer following disease progression on or after chemotherapy, according to the companies responsible for developing the agent, Seagen Inc. and Genmab A/S.

The decision from the agency is supported by data *from the single-arm phase 2 innovaTV 204 trial (NCT03438396) of tisotumab vedotin which resulted in a 24% (95% CI, 15.9%-33.3%) confirmed overall response rate by independent review committee in previously treated, recurrent or metastatic cervical cancer.*

"The journey towards the approval of Tivdak started nearly 2 decades ago with innovative research by scientists at Genmab and Seagen and reflects on our purpose of making an impact in the lives of [patients with] cancer and their families. Today's announcement marks Genmab's evolution into a fully integrated biotechnology company and we would like to thank patients, caregivers, investigators, and our collaborators for their participation in our clinical studies." Jan van de Winkel, PhD, chief executive officer of Genmab, said in a statement.

Results from the trial that were previously presented at the European Society for Medical Oncology 2020 Virtual Congress highlighted a 7% complete response rate and a 17% partial response rate, as well as a median duration of response (DOR) was 8.3 months (95% CI, 4.2–not reached). The biologics license application for tisotumab vedotin-tftv in this indication was submitted in February 2021 and granted priority review in April 2021. Continuous approval may be contingent upon verification from additional clinical data.

The phase 3 innovaTV 301 trial (NCT04697628) comparing tisotumab vedotin-tftc vs investigators choice of chemotherapy in patients with recurrent or metastatic cervical cancer is currently ongoing.

Reference

Seagen and Genmab announce FDA accelerated approval for TIVDAK™ (tisotumab vedotin-tftv) in previously treated recurrent or metastatic cervical cancer. News release. Seagen Inc. and Genmab A/S. September 20, 2021. Accessed September 20, 2021. https://bwnews.pr/2XJLowv

Lifileucel Plus Pembrolizumab Yields Positive ORR in Advanced Cancers

November 16, 2021

Ariana Pelosci

Patients with melanoma, head and neck squamous cell carcinoma, a*nd cervical cancer* who had not previously received immunotherapy and were treated with lifileucel plus pembrolizumab experienced promising overall response rates compared favorably with historical data on pembrolizumab monotherapy.

Lifileucel (LN-144), an autologous adoptive cell therapy that utilizes tumor infiltrating lymphocytes (TILs), plus pembrolizumab (Keytruda) led to promising overall response rates (ORRs), including some complete responses (CRs), for patients with immune *checkpoint inhibitor–naïve cervical cancer*, melanoma, and head and neck cancer, according to results of 2 phase 2 trials that were presented at the 2021 Society for Immunotherapy of Cancer (SITC) Annual Meeting.1,2

In cohort 3 of *the C-145-04 trial (NCT03108495*), *the ORR in 14 patients with persistent, recurrent, or metastatic cervical cancer* was 57.1%, which included 1 CR to lifileucel plus pembrolizumab.

In *the IOV-COM-202 study (NCT-3645928),* patients with advanced, recurrent, or metastatic melanoma who were treated in cohort 1A (n = 10) experienced an ORR of 60.0%, which included 3 CRs; those with advanced, recurrent, or metastatic head and

neck squamous cell carcinoma (HNSCC; n = 18) treated in cohort 2A experienced and ORR of 38.9%, including 1 CR. To be eligible for the trial, patients had to have 1 or more resectable lesions for TIL manufacturing, 1 or more measurable lesions for response assessment, and an ECOG performance status of 0 or 1.

Patients received 1 dose of pembrolizumab at either 200 mg or 400 mg after tumor resection but before nonmyeloablative lymphodepletion (NMA-LD), then went on to receive NMA-LD with cyclophosphamide at 60 mg/kg daily for 2 doses and fludarabine for 25 mg/m2 daily for 5 doses. Patients then received a TIL infusion between 1 × 109 to 150 × 109 cells, with less than 6 doses of interleukin-2 every 8 to 12 hours for up to 3 to 24 hours after completion of TIL infusions. Patients continued pembrolizumab every 3 weeks at 200 mg or 6 weeks at 400 mg for less than 24 months.

Three patients (30%) in cohort 1A and 12 (66.7%) in cohort 2A received chemotherapy as prior systemic therapy. In cohort 2A, 9 patients (50%) received radiotherapy. In cohort 3, 9 patients (64.3%) received curative or therapeutic surgery, 7 (50.0%) received chemo-radiotherapy, and 3 (21.4%) received radiotherapy only.

At study entry, 13 patients (72.2%) in cohort 2A and 13 (92.9%) in cohort 3 had M1 metastasis; in cohort 1A, 2 (20.0%) had M1A and 7 (70.0%) had M1C metastases. In cohort 1A, 4 patients (40.0%) had PD-L1 negative disease, defined by a tumor proportion score (TPS) below 5%, compared with 3 (16.7%) in cohort 2A and 1 (7.1%) in cohort 3. PD-L1 positivity, defined at TPS 5% or greater. was observed in 5 (50.0%), 11 (61.1%), and 10 (71.4%) patients, respectively.

Patients with melanoma experienced 100% tumor reduction, compared with 87.5% of patients with HNSCC and 85.7% with cervical cancer. These responses were durable and continued to deepen over time. At data cutoff, 4 out of 6 evaluable patients with melanoma (66.7%) had ongoing responses compared with 3 out of 6 (50.0%) with HNSCC, and 5 out of 7 (71.4%) with cervical cancer. The median study follow-up for those with melanoma was 11.5 months, 7.8 months for HNSCC, and 7.6 months for cervical cancer. Grade 3 or 4 treatment-emergent adverse effects (TEAEs) in all cohorts (N = 42) occurred in 95.2% of patients. One patient in cohort 1 (10.0%) and 4 (22.2%) in cohort 2 experienced grade 5 TEAEs. The most common grade 3 or 4 TEAEs were thrombocytopenia in 22 patients (52.4%), anemia in 21 (50.0%), and neutropenia in 17 (40.5%).

References

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2. O'Malley D, Lee S, Psyrri A, et al. Phase 2 efficacy and safety of autologous tumor-infiltrating lymphocyte (TIL) cell therapy in combination with pembrolizumab in immune checkpoint inhibitor-naïve patients with advanced cancer. Presented at 2021 Society for Immunotherapy of Cancer Annual Meeting. November 10-14, 2021, Washington DC. https://bit.ly/3nt1vsJ

KEYNOTE-826 Data in Cervical Cancer and Next Steps for Research

October 5, 2021

Maggie Tibbitt, Bradley J. Monk, MD, FACS, FACOG

Pembrolizumab (Keytruda) plus chemotherapy with or without bevacizumab (Avastin) resulted in a statistically significant and clinically meaningful improvement in overall survival (OS) and progression-free survival (PFS) in patients with persistent, recurrent, or metastatic cervical cancer. Results from the phase 3 KEYNOTE-826 (NCT04221945) showed that pembrolizumab plus chemotherapy with or without bevacizumab resulted in a median PFS of 10.4 months (95% CI, 9.1-12.1) vs 8.2 months (95% CI, 6.4-8.4) with chemotherapy with or without bevacizumab in the all-comer population (HR, 0.65; 95% CI, 0.53-0.79; P < .001).1 The median OS was 24.4 months (95% CI, 19.2–not reached) in the investigative arm vs 16.5 months (95% CI, 14.5-19.4) in the control arm (HR, 0.67; 95% CI, 0.54-0.84; P < .001).

At the first interim analysis of this study, which enrolled 617 patients, it basically met all the therapeutic end points. It wasn't underperformance of the control arm. The bevacizumab [arm] showed a response rate of 48% [vs 50.8%] in the control arm; 48% vs 50% are [very similar]. However, when pembrolizumab was added, the response rate increased to 66%.The HR for progression-free survival was 0.65.

No new safety signals were observed in the patient experience, and patient-reported outcomes look like they're better with the addition of pembrolizumab.

The median in the intervention arm has not been met. At 2 years, 33% more of the patients, or a HR of 0.67, are alive. At 2 years, half of the patients are still alive, which means half will live longer.

The accelerated approval of pembrolizumab in the second-line setting was restricted to PD-L1–positive patients with a CPS score of greater than 1.

KEYNOTE-826 was positive in all-comers and the 89% of the patients were PD-L1 positive. Eleven percent of patients were PD-L1 negative, and most of them had adenocarcinomas.

Reference

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