Libtayo® (cemiplimab) Approved by the European Commission as the First Immunotherapy in Second Line Recurrent or Metastatic Cervical Cancer Irrespective of PD-L1 Expression Level or Tumor Histology

November 22, 2022

Approval based on a Phase 3 trial that demonstrated significant survival benefit in patients with recurrent or metastatic cervical cancer, with Libtayo reducing the risk of death by 31% compared to chemotherapy during the study

Libtayo now approved to treat four cancer types in the European Union

TARRYTOWN, N.Y., Nov. 22, 2022 /PRNewswire/ -- Regeneron Pharmaceuticals, Inc. (NASDAQ: REGN) today announced that the European Commission (EC) approved Libtayo® (cemiplimab) as monotherapy for the treatment of adult patients with recurrent or metastatic cervical cancer and disease progression on or after platinum-based chemotherapy.

"Despite recent advancements in the prevention and treatment of cervical cancer, there remain limited options for people with recurrent or metastatic cases," said Israel Lowy, M.D., Ph.D., Senior Vice President, Translational and Clinical Sciences, Oncology at Regeneron. "Libtayo was the first PD-1 inhibitor to demonstrate significant improvements in survival compared to chemotherapy in a Phase 3 trial. With this fourth approval from the European Commission, Libtayo can now be extended to appropriate patients in the European Union with advanced cervical cancer, irrespective of their PD-L1 status or histology."

The EC approval in advanced cervical cancer is based on data from the global Phase 3 EMPOWER-Cervical 1 trial, which was conducted with the GOG Foundation, Inc. (GOG), the European Network for Gynaecological Oncological Trial groups (ENGOT) and NRG Oncology-Japan. The trial evaluated Libtayo in comparison to an investigator's choice of chemotherapy and enrolled 608 patients across 14 countries, irrespective of PD-L1 expression status or histology. In March 2021, the trial was stopped early based on the highly significant effect of Libtayo on overall survival (OS) among squamous cell carcinoma (SCC) patients following a unanimous recommendation by the Independent Data Monitoring Committee.

"Consistent with our mission to bring the best treatments to patients across Europe living with gynaecological cancers, we are proud to have been a part of the landmark ENGOT-cx9/GEICO/EMPOWER Cervical-1 trial for Libtayo," said Professor Ignace Vergote, investigator and gynecologist oncologist at University Hospitals Leuven in Belgium, and Vice-Chair of the Trial Steering Committee. "Libtayo is an important advancement for patients with recurrent or metastatic cervical cancer whose disease has progressed following platinum-based chemotherapy and could offer a new standard of care in this setting. We are grateful to those who participated in the trial and to our partners at Regeneron, ENGOT, the GOG Foundation and NRG Oncology-Japan without whom this approval would not have been possible."

Cervical cancer is the fourth leading cause of cancer death in women worldwide and is most frequently diagnosed between the ages of 35 and 44. Approximately 600,000 new cases of cervical cancer and 350,000 deaths from cervical cancer occur worldwide each year. Almost all cases are caused by human papillomavirus (HPV) infection, with approximately 80% classified as squamous cell carcinoma (SCC; arising from cells lining the external portion of the cervix) and the remainder largely adenocarcinomas (arising from glandular cells lining the internal portion of the cervix). Cervical cancer is often curable when detected early and effectively managed, but treatment options are more limited in advanced stages.

In addition to today's approval, Libtayo is approved in the European Union (EU) for the treatment of certain patients with advanced basal cell carcinoma (BCC), advanced cutaneous squamous cell carcinoma (CSCC) and advanced non-small cell lung cancer (NSCLC).

About the Phase 3 Trial
EMPOWER-Cervical 1 was an open-label, multi-center Phase 3 trial that investigated Libtayo monotherapy versus an investigator's choice of commonly used chemotherapy in patients with recurrent or metastatic cervical cancer who had progressed on platinum-based chemotherapy. Patients (median age: 51 years) were randomized to receive Libtayo (350 mg every three weeks) or chemotherapy (pemetrexed, vinorelbine, topotecan, irinotecan or gemcitabine). The primary endpoint for the trial was OS, analyzed first among patients with SCC, then in the total population.

Patients were allowed to enroll regardless of PD-L1 expression status, with 78% of patients having SCC and 22% having adenocarcinoma or adenosquamous carcinoma. The trial included women from 14 countries: Australia, Belgium, Brazil, Canada, Greece, Italy, Japan, Poland, Russia, South Korea, Spain, Taiwan, the UK and the U.S.

Results from the trial demonstrated that those treated with Libtayo (n=304) compared to chemotherapy (n=304) experienced significant improvements in OS, progression-free survival (PFS) and objective response rate (ORR) including a:

- 31% reduction in the risk of death and a longer median OS in the overall population (12.0 months Libtayo, 8.5 months chemotherapy; hazard ratio [HR]: 0.69; 95% confidence interval [CI]: 0.56 to 0.84; p=0.00011).
- 27% reduction in the risk of death and a longer median OS in patients with SCC histology (11.1 months Libtayo, 8.8 months chemotherapy; HR: 0.73; 95% CI: 0.58 to 0.91; p=0.00306).
- 25% reduction of risk in progressive disease in the overall population (HR: 0.75; 95% CI: 0.62 to 0.89; p=0.00048).
- 16% ORR for Libtayo, versus 6% for chemotherapy in the overall population (95% CI: 12.5 to 21.1 vs. 3.8 to 9.6).

Safety was assessed in 1,281 patients with advanced solid malignancies who received Libtayo monotherapy in five clinical studies. The median duration of exposure to Libtayo was 28 weeks (range: 2 days to 144 weeks). Immune-mediated adverse reactions occurred in 21% of patients treated

with Libtayo and led to permanent discontinuation in 4.6% of patients. The most common immune-mediated adverse reactions were hypothyroidism (6.8%), hyperthyroidism (3.0%), immune-mediated pneumonitis (2.6%), immune-mediated hepatitis (2.4%), immune-mediated colitis (2.0%) and immune-mediated skin adverse reactions (1.9%). Adverse events were serious in 32.4% of patients and led to permanent discontinuation in 9.4% of patients. The grade 3 or higher adverse events occurring in >1% of patients were anaemia (5.2%), hypertension (2.6%), fatigue (2.6%), urinary tract infection (2.3%), hepatitis (1.8%), musculoskeletal pain (1.8%), rash (1.6%) dyspnea (1.2%) and pneumonitis (1.1%). No new Libtayo safety signals were observed.

Results from the trial were previously published in the *New England Journal of Medicine*.

About Regeneron in Oncology
At Regeneron, we're applying more than three decades of scientific innovation with the goal of developing paradigm-changing therapies for patients with cancer. Our oncology portfolio is built around two foundational approaches – our approved PD-1 inhibitor Libtayo and investigational bispecific antibodies – which are being evaluated both as monotherapies and in combination with emerging therapeutic modalities. Together, they provide us with unique combinatorial flexibility to develop potentially synergistic treatments for a wide range of solid tumors and blood cancers.

If you are interested in learning more about our clinical trials, please contact us (clinicaltrials@regeneron.com or 844-734-6643) or visit our clinical trials website.

About Libtayo
Libtayo is a fully human monoclonal antibody targeting the immune checkpoint receptor PD-1 on T cells and was invented using Regeneron's proprietary *VelocImmune*® technology. By binding to PD-1, Libtayo has been shown to block cancer cells from using the PD-1 pathway to suppress T-cell activation. In the U.S. and other countries, Libtayo is indicated in certain patients with advanced basal cell carcinoma (BCC), advanced cutaneous squamous cell carcinoma (CSCC) and advanced non-small cell lung cancer (NSCLC), as well as in advanced cervical cancer in the EU, Canada and Brazil. As of July 1, 2022, Libtayo is developed and marketed globally by Regeneron.

In the U.S., the generic name for Libtayo in its approved indications is cemiplimab-rwlc, with rwlc as the suffix designated in accordance with Nonproprietary Naming of Biological Products Guidance for Industry issued by the U.S. Food and Drug Administration (FDA). Outside of the U.S. the generic name of Libtayo in its approved indication is cemiplimab.

The extensive clinical program for Libtayo is focused on difficult-to-treat cancers. Libtayo is currently being investigated in trials as a monotherapy, as well as in combination with either conventional or novel therapeutic approaches for other solid tumors and blood cancers. These potential uses are investigational, and their safety and efficacy have not been evaluated by any regulatory authority.

U.S. FDA-approved Indications
Libtayo is a prescription medicine used to treat:

- People with a type of skin cancer called cutaneous squamous cell carcinoma (CSCC) that has spread or cannot be cured by surgery or radiation.
- People with a type of skin cancer called basal cell carcinoma (BCC):
  - That cannot be removed by surgery (locally advanced BCC) and have received treatment with a hedgehog pathway inhibitor (HHI), or cannot receive treatment with an HHI.
  - That has spread (metastatic BCC) and have received treatment with an HHI, or cannot receive treatment with an HHI. This use is approved based on how many patients responded to treatment and how long they responded. Studies are ongoing to provide additional information about clinical benefit.
- Adults with a type of lung cancer called NSCLC:
  - Libtayo may be used in combination with chemotherapy that contains a platinum medicine as your first treatment when your lung cancer has not spread outside your chest (locally advanced lung cancer) and you cannot have surgery or chemotherapy with radiation, OR your lung cancer has spread to other areas of your body (metastatic lung cancer), AND your tumor does not have an abnormal "EGFR", "ALK" or "ROS1" gene.
  - Libtayo may be used alone as your first treatment when your lung cancer has not spread outside your chest (locally advanced lung cancer) and you cannot have surgery or chemotherapy with radiation, OR your lung cancer has spread to other areas of your body (metastatic lung cancer), AND your tumor tests positive for high "PD-L1", AND your tumor does not have an abnormal "EGFR", "ALK "or "ROS1" gene.

It is not known if Libtayo is safe and effective in children.

About Regeneron's *VelocImmune* Technology
Regeneron's *VelocImmune* technology utilizes a proprietary genetically engineered mouse platform endowed with a genetically humanized immune system to produce optimized fully human antibodies. When Regeneron's co-Founder, President and Chief Scientific Officer George D. Yancopoulos was a graduate student with his mentor Frederick W. Alt in 1985, they were the first to envision making such a genetically humanized mouse, and Regeneron has spent decades inventing and developing *VelocImmune* and related *VelociSuite*® technologies. Dr. Yancopoulos and his team have used *VelocImmune* technology to create approximately one in five of all original, FDA-approved or authorized fully human monoclonal antibodies. This includes REGEN-COV® (casirivimab and imdevimab), Dupixent® (dupilumab), Libtayo® (cemiplimab-rwlc), Praluent® (alirocumab), Kevzara® (sarilumab), Evkeeza® (evinacumab-dgnb) and Inmazeb® (atoltivimab, maftivimab and odesivimab-ebgn).

IMPORTANT SAFETY INFORMATION FOR U.S. PATIENTS

What is the most important information I should know about Libtayo?
LIBTAYO is a medicine that may treat certain cancers by working with your immune system. LIBTAYO can cause your immune system to attack normal organs and tissues in any area of your body and can affect the way they work. These problems can sometimes become severe or life-threatening and

can lead to death. You can have more than one of these problems at the same time. These problems may happen anytime during treatment or even after your treatment has ended.

Call or see your healthcare provider right away if you develop any new or worsening signs or symptoms, including:

- **Lung problems:** cough, shortness of breath, or chest pain
- **Intestinal problems:** diarrhea (loose stools) or more frequent bowel movements than usual, stools that are black, tarry, sticky or have blood or mucus, or severe stomach-area (abdomen) pain or tenderness
- **Liver problems:** yellowing of your skin or the whites of your eyes, severe nausea or vomiting, pain on the right side of your stomach area (abdomen), dark urine (tea colored), or bleeding or bruising more easily than normal
- **Hormone gland problems:** headache that will not go away or unusual headaches, eye sensitivity to light, eye problems, rapid heartbeat, increased sweating, extreme tiredness, weight gain or weight loss, feeling more hungry or thirsty than usual, urinating more often than usual, hair loss, feeling cold, constipation, your voice gets deeper, dizziness or fainting, or changes in mood or behavior, such as decreased sex drive, irritability, or forgetfulness
- **Kidney problems:** decrease in your amount of urine, blood in your urine, swelling of your ankles, or loss of appetite
- **Skin problems:** rash, itching, skin blistering or peeling, painful sores or ulcers in mouth or nose, throat, or genital area, fever or flu-like symptoms, or swollen lymph nodes
- **Problems can also happen in other organs and tissues. These are not all of the signs and symptoms of immune system problems that can happen with LIBTAYO. Call or see your healthcare provider right away for any new or worsening signs or symptoms, which may include:** chest pain, irregular heartbeat, shortness of breath or swelling of ankles, confusion, sleepiness, memory problems, changes in mood or behavior, stiff neck, balance problems, tingling or numbness of the arms or legs, double vision, blurry vision, sensitivity to light, eye pain, changes in eyesight, persistent or severe muscle pain or weakness, muscle cramps, low red blood cells, or bruising
- **Infusion reactions that can sometimes be severe.** Signs and symptoms of infusion reactions may include: nausea, chills or shaking, itching or rash, flushing, shortness of breath or wheezing, dizziness, feel like passing out, fever, back or neck pain, or facial swelling
- **Rejection of a transplanted organ.** Your healthcare provider should tell you what signs and symptoms you should report and monitor you, depending on the type of organ transplant that you have had
- **Complications, including graft-versus-host disease (GVHD), in people who have received a bone marrow (stem cell) transplant that uses donor stem cells (allogeneic).** These complications can be serious and can lead to death. These complications may happen if you underwent transplantation either before or after being treated with LIBTAYO. Your healthcare provider will monitor you for these complications

Getting medical treatment right away may help keep these problems from becoming more serious. Your healthcare provider will check you for these problems during your treatment with LIBAYO. Your healthcare provider may treat you with corticosteroid or hormone replacement medicines. Your healthcare provider may also need to delay or completely stop treatment with LIBTAYO if you have severe side effects.

Before you receive Libtayo, tell your healthcare provider about all your medical conditions, including if you:

- have immune system problems such as Crohn's disease, ulcerative colitis, or lupus
- have received an organ transplant
- have received or plan to receive a stem cell transplant that uses donor stem cells (allogeneic)
- have received radiation treatment to your chest area
- have a condition that affects your nervous system, such as myasthenia gravis or Guillain-Barré syndrome
- are pregnant or plan to become pregnant. LIBTAYO can harm your unborn baby

Females who are able to become pregnant:

- Your healthcare provider will give you a pregnancy test before you start treatment
- You should use an effective method of birth control during your treatment and for at least 4 months after your last dose of LIBTAYO. Talk with your healthcare provider about birth control methods that you can use during this time
- Tell your healthcare provider right away if you become pregnant or think you may be pregnant during treatment with LIBTAYO
- are breastfeeding or plan to breastfeed. It is not known if LIBTAYO passes into your breast milk. Do not breastfeed during treatment and for at least 4 months after the last dose of LIBTAYO

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

The most common side effects of LIBTAYO when used alone include muscle or bone pain, tiredness, rash, and diarrhea. The most common side effects of LIBTAYO when used in combination with platinum-containing chemotherapy include hair loss, muscle or bone pain, nausea, tiredness, numbness, pain, tingling, or burning in your hands or feet, decreased appetite. These are not all the possible side effects of LIBTAYO. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088. You may also report side effects to Regeneron Pharmaceuticals at 1-877-542-8296.

Please see full Prescribing Information, including Medication Guide.

About Regeneron
Regeneron is a leading biotechnology company that invents, develops and commercializes life-transforming medicines for people with serious diseases. Founded and led for nearly 35 years by physician-scientists, our unique ability to repeatedly and consistently translate science into medicine has led to nine FDA-approved treatments and numerous product candidates in development, almost all of which were homegrown in our laboratories. Our medicines and pipeline are designed to help patients with eye diseases, allergic and inflammatory diseases, cancer, cardiovascular and metabolic diseases, pain, hematologic conditions, infectious diseases and rare diseases.

Regeneron is accelerating and improving the traditional drug development process through our proprietary *VelociSuite* technologies, such as *VelocImmune*, which uses unique genetically humanized mice to produce optimized fully human antibodies and bispecific antibodies, and through ambitious research initiatives such as the Regeneron Genetics Center®, which is conducting one of the largest genetics sequencing efforts in the world.

For more information, please visit www.Regeneron.com or follow @Regeneron on Twitter.

Forward-Looking Statements and Use of Digital Media
This press release includes forward-looking statements that involve risks and uncertainties relating to future events and the future performance of Regeneron Pharmaceuticals, Inc. ("Regeneron" or the "Company"), and actual events or results may differ materially from these forward-looking statements. Words such as "anticipate," "expect," "intend," "plan," "believe," "seek," "estimate," variations of such words, and similar expressions are intended to identify such forward-looking statements, although not all forward-looking statements contain these identifying words. These statements concern, and these risks and uncertainties include, among others, the impact of SARS-CoV-2 (the virus that has caused the COVID-19 pandemic) on Regeneron's business and its employees, collaborators, and suppliers and other third parties on which Regeneron relies, Regeneron's and its collaborators' ability to continue to conduct research and clinical programs, Regeneron's ability to manage its supply chain, net product sales of products marketed or otherwise commercialized by Regeneron and/or its collaborators or licensees (collectively, "Regeneron's Products"), and the global economy; the nature, timing, and possible success and therapeutic applications of Regeneron's Products and product candidates being developed by Regeneron and/or its collaborators or licensees (collectively, "Regeneron's Product Candidates") and research and clinical programs now underway or planned, including without Libtayo® (cemiplimab) for the treatment of adult patients with recurrent or metastatic cervical cancer and disease progression on or after platinum-based chemotherapy; uncertainty of the utilization, market acceptance, and commercial success of Regeneron's Products and Regeneron's Product Candidates and the impact of studies (whether conducted by Regeneron or others and whether mandated or voluntary), including the studies discussed or referenced in this press release, on any of the foregoing; the likelihood, timing, and scope of possible regulatory approval and commercial launch of Regeneron's Product Candidates and new indications for Regeneron's Products, such as Libtayo (as a monotherapy or in combination with conventional or novel therapeutic approaches, as applicable) for other solid tumors and blood cancers as well as Regeneron's investigational bispecific antibodies referenced in this press release; safety issues resulting from the administration of Regeneron's Products (such as Libtayo) and Regeneron's Product Candidates in patients, including serious complications or side effects in connection with the use of Regeneron's Products and Regeneron's Product Candidates in clinical trials; determinations by regulatory and administrative governmental authorities which may delay or restrict Regeneron's ability to continue to develop or commercialize Regeneron's Products and Regeneron's Product Candidates; ongoing regulatory obligations and oversight impacting Regeneron's Products, research and clinical programs, and business, including those relating to patient privacy; the availability and extent of reimbursement of Regeneron's Products (such as Libtayo) from third-party payers, including private payer healthcare and insurance programs, health maintenance organizations, pharmacy benefit management companies, and government programs such as Medicare and Medicaid; coverage and reimbursement determinations by such payers and new policies and procedures adopted by such payers; competing drugs and product candidates that may be superior to, or more cost effective than, Regeneron's Products and Regeneron's Product Candidates; the extent to which the results from the research and development programs conducted by Regeneron and/or its collaborators or licensees (including those discussed or referenced in this press release) may be replicated in other studies and/or lead to advancement of product candidates to clinical trials or therapeutic applications; the ability of Regeneron to manufacture and manage supply chains for multiple products and product candidates; the ability of Regeneron's collaborators, licensees, suppliers, or other third parties (as applicable) to perform manufacturing, filling, finishing, packaging, labeling, distribution, and other steps related to Regeneron's Products and Regeneron's Product Candidates; unanticipated expenses; the costs of developing, producing, and selling products; the ability of Regeneron to meet any of its financial projections or guidance and changes to the assumptions underlying those projections or guidance; the potential for any license or collaboration agreement, including Regeneron's agreements with Sanofi and Bayer (or their respective affiliated companies, as applicable), to be cancelled or terminated; and risks associated with intellectual property of other parties and pending or future litigation relating thereto (including without limitation the patent litigation and other related proceedings relating to EYLEA® (aflibercept) Injection, Praluent® (alirocumab), and REGEN-COV® (casirivimab and imdevimab)), other litigation and other proceedings and government investigations relating to the Company and/or its operations, the ultimate outcome of any such proceedings and investigations, and the impact any of the foregoing may have on Regeneron's business, prospects, operating results, and financial condition. A more complete description of these and other material risks can be found in Regeneron's filings with the U.S. Securities and Exchange Commission, including its Form 10-K for the year ended December 31, 2021 and its Form 10-Q for the quarterly period ended September 30, 2022. Any forward-looking statements are made based on management's current beliefs and judgment, and the reader is cautioned not to rely on any forward-looking statements made by Regeneron. Regeneron does not undertake any obligation to update (publicly or otherwise) any forward-looking statement, including without limitation any financial projection or guidance, whether as a result of new information, future events, or otherwise.

Regeneron uses its media and investor relations website and social media outlets to publish important information about the Company, including information that may be deemed material to investors. Financial and other information about Regeneron is routinely posted and is accessible on Regeneron's media and investor relations website (http://newsroom.regeneron.com) and its Twitter feed (http://twitter.com/regeneron).

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