Libtayo® (cemiplimab-rwlc) in Combination with Chemotherapy Approved by the FDA as First-line Treatment for Advanced Non-small Cell Lung Cancer (NSCLC)

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Approval based on superior survival outcomes of Libtayo plus chemotherapy, compared to chemotherapy alone, in a patient population with a wide range of disease characteristics

Second advanced NSCLC indication expands patient population eligible for a Libtayo-based regimen to include combination treatment with chemotherapy irrespective of PD-L1 expression levels

TARRYTOWN, N.Y., Nov. 8, 2022 /PRNewswire/ -- Regeneron Pharmaceuticals, Inc. (NASDAQ: REGN) today announced that the U.S. Food and Drug Administration (FDA) has approved the PD-1 inhibitor Libtayo® (cemiplimab-rwlc) in combination with platinum-based chemotherapy for the first-line treatment of adult patients with advanced non-small cell lung cancer (NSCLC) with no EGFR, ALK or ROS1 aberrations. Patients must either have metastatic or locally advanced tumors that are not candidates for surgical resection or definitive chemoradiation. Patients may be treated with this combination irrespective of PD-L1 expression or histology.

"This second FDA approval for cemiplimab-rwlc in advanced non-small cell lung cancer greatly broadens the scope in which a cemiplimab-rwlc-based regimen can be prescribed to encompass a wide range of patients, either as single agent in those with PD-L1 ≥50% or now in combination with chemotherapy irrespective of PD-L1 expression or tumor histology," said David R. Gandara, M.D., Professor Emeritus and Senior Advisor of the Thoracic Oncology Program at the University of California Davis Comprehensive Cancer Center. "The approval is based on a Phase 3 trial designed to closely resemble a patient population with varied disease presentations that physicians manage in everyday clinical practice. Even with these diverse disease presentations, cemiplimab-rwlc combined with chemotherapy demonstrated a marked increase in overall survival, at a median of 22 months versus 13 months with chemotherapy alone. Clearly, this is an advance which is clinically meaningful for our patients with advanced stage non-small cell lung cancer."

The FDA approval is based on data from the global Phase 3 trial, EMPOWER-Lung 3, that investigated Libtayo in combination with a physician's choice of platinum-doublet chemotherapy (Libtayo combination), compared to platinum-doublet chemotherapy alone. The trial enrolled 466 patients with locally advanced or metastatic NSCLC, irrespective of PD-L1 expression or tumor histology, and with no ALK, EGFR or ROS1 aberrations. Among those enrolled, 43% had tumors with squamous histology, 67% had tumors with <50% PD-L1 expression, 15% had inoperable locally advanced disease not eligible for definitive chemoradiation, and 7% had pretreated and clinically stable brain metastases.

"Libtayo is now approved for extending the survival of patients with advanced non-small cell lung cancer as both a monotherapy in high PD-L1 expressors and in combination with chemotherapy irrespective of PD-L1 expression levels, achieving a high bar that has only been met by one other PD-1 targeting agent," said Israel Lowy, M.D., Ph.D., Senior Vice President, Translational and Clinical Sciences, Oncology at Regeneron. "With this FDA approval, Libtayo can expand its role as a key treatment option for advanced non-small lung cancer, in addition to serving as a standard-of-care for two advanced non-melanoma skin cancers. We are committed to investigating Libtayo through ongoing trials as a monotherapy and as a backbone of combination treatments in multiple cancers. We thank the many investigators, patients and their families who have participated in our pivotal trials."

Efficacy in EMPOWER-Lung 3 was assessed in 466 patients who were randomized 2:1 to receive either Libtayo 350 mg (n=312) or placebo (n=154) intravenously every 3 weeks, plus histology-specific platinum-doublet chemotherapy. The trial was stopped early based on a recommendation by the Independent Data Monitoring Committee after the Libtayo combination demonstrated a significant improvement in overall survival (OS), the primary endpoint. Efficacy results comparing the Libtayo combination to chemotherapy alone showed a:

- **22-month median OS** versus 13 months, representing a 29% relative reduction in the risk of death (hazard ratio [HR]: 0.71; 95% confidence interval [CI]: 0.53 to 0.93; p=0.014). The 12-month probability of survival was 66% for the Libtayo combination versus 56% for chemotherapy, per Kaplan-Meier estimates.
- **8-month median PFS** versus 5 months, representing a 44% reduction in the risk of disease progression (HR: 0.56; 95% CI: 0.44 to 0.70; p<0.0001). The 12-month probability of PFS for the Libtayo combination was 38% versus 16% for chemotherapy.
- **43% overall response rate** versus 23%.
- **16-month median DOR** (range: 2 to 19+) versus 7 months (range: 2 to 19+).

Safety was assessed in 312 patients in the Libtayo combination group (median duration of exposure: 38 weeks) and 153 patients

in the chemotherapy group (median duration of exposure: 21 weeks). The most common adverse reactions occurring in >15% of patients were alopecia (37% Libtayo combination, 43% placebo), musculoskeletal pain (30% Libtayo combination, 36% placebo), nausea (25% Libtayo combination, 16% placebo), fatigue (23% Libtayo combination, 18% placebo), peripheral neuropathy (23% Libtayo combination, 19% placebo) and decreased appetite (17% Libtayo combination, 12% placebo). Serious adverse reactions occurred in 25% of patients, with treatment discontinuations due to adverse reactions in 5% and fatal adverse reactions in 6%. No new Libtayo safety signals were observed.

"The approval of Libtayo in the combination setting builds on the monotherapy indication in advanced non-small cell lung cancer and furthers our excitement for what's to come as we continue our potentially transformative oncology research," said George D. Yancopoulos, M.D., Ph.D., President and Chief Scientific Officer at Regeneron. "Libtayo is the backbone of our oncology strategy, designed to synergistically combine multiple modalities to provide more options for more patients. We look forward to delivering on the promise of our research in other meaningful combinations that leverage Libtayo and our homegrown pipeline of investigational bispecific antibodies."

"We welcome this latest approval for Libtayo as a first-line combination treatment for appropriate patients with advanced lung cancer," said Andrea Ferris, President and CEO at the LUNGevity Foundation. "Lung cancer remains one of the most common cancers worldwide, and every new treatment option is an important step forward against this deadly cancer."

About Non-small Cell Lung Cancer (NSCLC)
Lung cancer is the leading cause of cancer death worldwide. In recent years, more than 236,000 and 2.2 million annual new cases have been diagnosed in the U.S. and globally, respectively. Approximately 84% of all lung cancers are NSCLC, with 75% of these cases diagnosed in advanced stages. Additionally, 70% of all NSCLC cases will have <50% PD-L1 expression, making it the most common treatment setting.

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 NSCLC, as well as in advanced cervical cancer in Canada and Brazil. As of July 1, 2022, Libayo 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 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 advanced 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.

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 LIBTAYO. 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'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, Praluent® (alirocumab), Kevzara® (sarilumab), Evkeeza® (evinacumab-dgnb) and Inmazeb™ (atoltivimab, maftivimab and odesivimab-ebgn).

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.

Regeneron 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-rwlc) in combination with chemotherapy for the treatment of advanced non-small cell lung cancer; 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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