Fianlimab (LAG-3 inhibitor) Combined with Libtayo® (cemiplimab) Shows Clinically Meaningful and Durable Tumor Responses Across Key Advanced Melanoma Patient Populations

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Data demonstrate objective response rates from 56% to 63% across three independent cohorts of advanced melanoma patients – about double the rate historically seen with anti-PD-1 alone in similar settings – per trial results to be presented in an oral session at ASCO

Clinically meaningful responses observed in post hoc analyses of populations of interest, including patients with poor prognosis factors, prior anti-PD-1 therapy in the adjuvant setting and varying tumor PD-L1 expression levels

Pivotal Phase 3 trials in adjuvant and first-line advanced melanoma underway

TARRYTOWN, N.Y., May 25, 2023 (GLOBE NEWSWIRE) -- Regeneron Pharmaceuticals, Inc. (NASDAQ: REGN) today announced positive data from three independent cohorts evaluating an investigational combination of LAG-3 inhibitor fianlimab and PD-1 inhibitor Libtayo® (cemiplimab) in adults with advanced melanoma. The early clinical trial results, which demonstrated the combination led to clinically meaningful and durable results across multiple clinical settings, will be shared in an oral session at the 2023 American Society of Clinical Oncology (ASCO) Annual Meeting in Chicago on Monday, June 5 at 3:00 PM CT.

“LAG-3 inhibitors are known to complement PD-1 inhibitors in the treatment of advanced melanoma. There exists an unmet need to further improve the benefit to patients, including those with liver metastases and other high-risk prognostic markers,” said Omid Hamid, M.D., Director, Clinical Research and Immunotherapy at The Angeles Clinic and Research Institute, and principal investigator of the trial. “These updated and independent expansion cohort results reinforce the potential of the fianlimab and cemiplimab (Libtayo) combination to deliver clinically meaningful and durable responses in diverse clinical settings and patient populations, with an acceptable safety profile. Particularly encouraging is that the clinical activity was observed in post hoc analyses of patient subgroups, including in patients with a poor prognosis or those who had been previously treated with an anti-PD-1 therapy in the adjuvant setting.”

The data to be presented at ASCO 2023 include findings from three independent expansion cohorts of adults with unresectable or metastatic melanoma who were all naïve to anti-PD-1 therapy for advanced disease (n=98). Additional follow up will be reported on an initial cohort of first- or second-line patients (n=40) and a confirmatory cohort of first-line patients (n=40), previously reported at ESMO 2022. New for this presentation is a cohort of patients who had received prior systemic treatment for melanoma in the neoadjuvant or adjuvant setting (n=18), including adjuvant anti-PD-1 therapy (n=13 of 18).

Tumor responses were based on RECIST 1.1 criteria and per investigator assessment. The median duration of response (DOR) was not reached in any cohort, and the objective response rate (ORR) by cohort was as follows:

- **Initial cohort:** 63% (25 of 40 patients), including 6 complete responses (CR) and 19 partial responses (PR).
- **Confirmatory cohort:** 63% (25 of 40 patients), including 5 CRs and 20 PRs.
- **Prior neo/adjuvant systemic therapy cohort:** 56% (10 of 18 patients). Among the 13 patients in this latest cohort who had **prior anti-PD-1 adjuvant treatment**, the ORR was 62% (8 of 13 patients), including 1 CR and 7 PRs.

In a post hoc analysis of the three combined cohorts, the ORR was 61% (60 of 98 patients), the median progression-free survival (PFS) was 15 months per Kaplan-Meier estimate (95% CI: 9–NE), and the median follow-up was 13 months (interquartile range 9-19). Additional post hoc analyses found clinically meaningful activity in multiple subgroups of interest, with ORRs in each as follows:

- **Poor prognosis:** 53% (17 of 32 patients) in cases with high baseline lactate dehydrogenase (LDH), 43% (9 of 21 patients) in cases of liver metastasis, and 35% (6 of 17 patients) in cases of M1c stage (visceral metastatic) disease and high baseline LDH.
- **Varying tumor PD-L1 expression levels:** 73% (19 of 26 patients) in cases of ≥1% PD-L1 expression and 56% (23 of 41 patients) in cases of <1% PD-L1 expression.

The safety profile of the fianlimab and Libtayo combination in these expansion cohorts appeared to be generally consistent with the safety profile of Libtayo monotherapy and other anti-PD-(L)1 agents, except for higher rates of adrenal insufficiency, which were ≤Grade 2 in the majority of cases (64%) and all cases were successfully managed with steroid replacement. Adverse events (AEs) occurred in 94% of patients, with 44% being ≥Grade 3 and 30% considered serious. AEs occurring in ≥10% of patients included rash (20%), pruritis (16%), diarrhea (15%), arthralgia (13%), hypothyroidism (12%), adrenal insufficiency (11%) and myalgia (10%). The treatment discontinuation rate due to AEs was 16%.

“Fianlimab in combination with Libtayo has now demonstrated robust response rates in three independent advanced melanoma cohorts – each with unique patient populations,” said Israel Lowy, M.D., Ph.D., Senior Vice President, Translational and Clinical Sciences, Oncology at Regeneron. “These positive results support the clinical potential of fianlimab in combination with Libtayo. We look forward to partnering with the oncology community to further investigate this combination in a broad pivotal clinical development program that includes Phase 3 trials in the advanced and adjuvant melanoma settings, alongside ongoing Phase 2/3 trials in non-small cell lung cancer and research in other solid tumors.”

Additional presentations on the fianlimab and Libtayo combination will be shared at ASCO during a poster session on Saturday, June 3 from 1:15 to 4:15 PM CT, including:

- A Phase 1 study of fianlimab (anti-LAG-3) in combination with cemiplimab (anti-PD-1) in patients with advanced melanoma: poor prognosis subgroup analysis (#9548)
- A Phase 3 trial of fianlimab (anti-LAG-3) plus cemiplimab (anti-PD-1) versus pembrolizumab in patients with previously untreated unresectable locally advanced or metastatic melanoma (#TPS9602)
- A Phase 3 trial comparing fianlimab (anti-LAG-3) plus cemiplimab (anti-PD-1) to pembrolizumab in patients with completely resected high-risk melanoma (#TPS9598)

The potential use of fianlimab and Libtayo described above is investigational, and safety and efficacy of this combination have not been evaluated by any regulatory authority.

About Regeneron's Approach to Cancer Research
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 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 the Phase 1 Trial
The Phase 1 trial is a first-in-human, multi-cohort study investigating fianlimab in combination with Libtayo in patients with advanced melanoma. The primary endpoint is ORR per RECIST 1.1 criteria; secondary endpoints include PFS, DOR, disease control rate (DCR), safety and pharmacokinetics (PK).

In these three expansion cohorts, 98 patients were enrolled and received fianlimab 1600 mg and Libtayo 350 mg intravenously every 3 weeks for up to 51 weeks, with a median follow up of 12.6 months and median treatment duration of 32.9 weeks. Additional analyses from the Phase 1 trial are ongoing.

About fianlimab
Fianlimab is a fully human monoclonal antibody targeting the immune checkpoint receptor LAG-3 on T cells and was invented using Regeneron's proprietary *VelocImmune*® technology. In melanoma, LAG-3 expression on cancer cells is associated with therapeutic resistance to PD-1 inhibitors. Fianlimab is being investigated in combination with Regeneron's PD-1 inhibitor Libtayo to determine whether concurrent blockade of LAG-3 and PD-1 can help overcome this resistance and release the brakes on T cell activation.

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 the European Union, 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) when your BCC cannot be removed by surgery (locally advanced BCC) or when it has spread (metastatic BCC) and have received treatment with a hedgehog pathway inhibitor (HHI), or cannot receive treatment with a HHI.
- Adults with a type of lung cancer called non-small cell lung cancer (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 or life-threatening.** Signs and symptoms of infusion reactions may include: nausea, vomiting, 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 to 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 tiredness, muscle or bone pain, rash, diarrhea, and low levels of red blood cells (anemia). 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, and 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 a substantial proportion 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 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 nature, timing, and possible success and therapeutic applications of products marketed or otherwise commercialized by Regeneron and/or its collaborators or licensees (collectively, "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 limitation fianlimab in combination with Libtayo® (cemiplimab); the likelihood, timing, and scope of possible regulatory approval and commercial launch of Regeneron's Product Candidates and new indications for Regeneron's Products, including fianlimab in combination with Libtayo for the treatment of advanced melanoma as well as Libtayo (as a monotherapy or in combination with conventional or novel therapeutic approaches, as applicable) for other solid tumors and blood cancers and Regeneron's investigational bispecific antibodies referenced in this press release; 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 or any potential regulatory approval of Regeneron's Products and Regeneron's Product Candidates (such as fianlimab); 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; the ability of Regeneron to manage supply chains for multiple products and product candidates; safety issues resulting from the administration of Regeneron's Products 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 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 may be replicated in other studies and/or lead to advancement of product candidates to clinical trials, therapeutic applications, or regulatory approval; 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, collaboration, or supply agreement, including Regeneron's agreements with Sanofi and Bayer (or their respective affiliated companies, as applicable) to be cancelled or terminated; the impact of public health outbreaks, epidemics, or pandemics (such as the COVID-19 pandemic) on Regeneron's business; 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, 2022 and its Form 10-Q for the quarterly period ended March 31, 2023. 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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