New Publication Highlights Preclinical Research Showing Potential to Enhance Cancer Treatment by Combining Novel Costimulatory Bispecific Antibodies with Libtayo® (cemiplimab)

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First publication to demonstrate benefit of combining CD28 costimulatory bispecifics with anti-PD-1 therapy, overcoming resistance to anti-PD-1 monotherapy and endowing long-term T-cell memory in multiple preclinical cancer models

An earlier publication highlighted benefit of combining CD28 costimulatory bispecifics with CD3 bispecifics for prostate and ovarian cancers

Regeneron anticipates having three CD28 costimulatory bispecifics in the clinic by the end of 2020

Regeneron Pharmaceuticals, Inc. (NASDAQ: **REGN**) announced new scientific findings have been highlighted today in a *Science Translational Medicine* cover publication. The preclinical research in animal models found that combining Regeneron's novel class of CD28 costimulatory bispecific antibodies with the anti-PD-1 therapy Libtayo® (cemiplimab) markedly enhanced anti-tumor activity in multiple cancer models, led to long-term T-cell memory against the tumors, and was not associated with systemic cytokine release.

CD28 offers a well-known and powerful pathway to fully activate T-cells. Regeneron's CD28 costimulatory bispecifics are designed to bridge T-cells to cancers cells, thereby selectively activating T-cells at the tumor site via the CD28 pathway and synergistically enhancing the anti-tumor activity of anti-PD-1 therapies and/or CD3 bispecifics. The potential of this therapeutic approach has now been featured on two *Science Translational Medicine* covers, including a prior publication in January 2020 that highlighted the benefit of combining CD28 costimulatory bispecifics with CD3 bispecifics for prostate and ovarian cancers.

As detailed in the new *Science Translational Medicine* paper, combining CD28 costimulatory bispecifics with Libtayo for prostate or other epithelial cancers led to synergistic increases in tumor-killing by T-cells in animal models and cell cultures. Most importantly, the combination overcame the resistance of both cancers to anti-PD-1 monotherapy. In addition, T-cells acquired long-term memory of the cancers after treatment, as demonstrated by genetic analyses of T-cells and successfully re-challenging mice with tumors following initial treatment with the combination. This long-term T-cell immune memory was limited when Libtayo was administered alone.

"Preclinical research shows that when combined with other immunotherapies, our novel CD28 costimulatory bispecifics can trigger targeted tumor killing in cancers that are generally resistant to current monotherapy regimens," said Dimitris Skokos, Ph.D., Senior Director, Cancer Immunology Research at Regeneron. "Adding CD28 costimulatory bispecifics to Libtayo activated T-cells against tumors more deeply and durably than Libtayo treatment alone. In addition, we did not observe systemic cytokine release syndrome in our animal studies. Systemic cytokine release has historically been a challenge with CD28 superagonists."

Regeneron's decision to develop novel CD28 costimulatory bispecifics was based on the knowledge that T-cells' ability to kill cancer is controlled by numerous stimulatory and inhibitory signals. T-cells must receive at least two different stimulatory signals to become fully activated for cancer killing. The first stimulatory signal is received when T-cells "recognize" foreign proteins on the cancer cell via the T-cell receptor/CD3 complex. This enables T-cells to optimally respond to the second "costimulatory" signal, which occurs most powerfully when T-cell CD28 costimulatory receptors interact with antigen presenting cells.

In 2020, Regeneron plans to enroll patients in clinical trials investigating three different CD28 costimulatory bispecific candidates. Regeneron's first costimulatory bispecific trial, investigating the combination of PSMAxCD28 (REGN5678) and Libtayo for prostate cancer, is underway and has treated patients in several dose-escalation cohorts. Before the end of the year, Regeneron plans to begin a clinical trial with EGFRxCD28 (REGN7075) and Libtayo in solid tumors that may include non-small cell lung cancer, head and neck squamous cell carcinoma, cutaneous squamous cell carcinoma and colorectal cancer. Another clinical trial will investigate MUC16xCD28 (REGN5668) in combination with either Libtayo or MUC16xCD3 (REGN4018) for ovarian cancer.

"Our novel CD28 costimulatory bispecifics are designed to be customized to target a diverse range of antigens, potentially enhancing treatment for multiple cancers," said Israel Lowy, M.D., Ph.D., Senior Vice President, Translational and Clinical Sciences, Oncology, at Regeneron. "Given these impressive preclinical findings, we are advancing multiple CD28 costimulatory bispecifics into the clinic. We hope to share initial data from our prostate cancer trial investigating REGN5678 in combination with Libtayo in 2021."

About the Regeneron Bispecific Antibody Platform
All of Regeneron's bispecifics are designed to closely resemble natural human antibodies and bind to two different targets. They are derived from a next-generation version of Regeneron's proprietary *VelocImmune* technology and created using the company's *Veloci-Bi*® platform. These allow for the creation of bispecifics with no linkers or artificial sequences. Additionally, Regeneron bispecifics are manufactured using similar approaches used for human antibody medicines, with similar pharmacokinetics.

There are eight Regeneron investigational bispecific antibodies for multiple blood cancers and solid tumors that will be in clinical trials by the end of the year. These bispecifics fall into three categories:

- **CD3 bispecifics** are designed to bridge T-cells and tumor cells. At the tumor site, they activate T-cells via their CD3 receptors and promote T-cell killing of the cancer cells. Investigational candidates include:

    - CD20xCD3 (odronextamab) for non-Hodgkin B-cell lymphomas;
    - Two distinct BCMAxCD3s (REGN5458 and REGN5459) for multiple myeloma;
    - MUC16xCD3 (REGN4018) for ovarian cancer.
- **CD28 costimulatory bispecifics** are also designed to bridge T-cells and tumor cells. At the tumor site, they costimulate T-cells via their CD28 receptors and may synergize with anti-PD-1 therapies and/or CD3 bispecifics. Investigational candidates include:
    - PSMAxCD28 (REGN5678) in combination with Libtayo for prostate cancer;
    - MUC16xCD28 (REGN5668) in combination with Libtayo for ovarian cancer;
    - EGFRxCD28 (REGN7075) in combination with Libtayo for solid tumors.
- **Tumor-targeted bispecifics** are designed to target proteins only on the cancer cell. In this way, they may affect various signaling pathways to hamper the cancer cells' ability to survive and proliferate. Investigational candidates include:
    - METxMET(REGN5093) for non-small cell lung cancer that is driven by MET mutations and/or amplifications. REGN5093 targets two different parts of the MET receptor on cancer cells to degrade the receptor and block its ability to trigger cell proliferation.

The bispecifics mentioned in this release are currently under clinical development, and their safety and efficacy have not been evaluated by any regulatory authority. As part of a global collaboration agreement, Regeneron and Sanofi are jointly developing the BCMAxCD3 and MUC16xCD3 bispecific programs.

About Libtayo
Libtayo is a fully-human monoclonal antibody targeting the immune checkpoint receptor PD-1 on T-cells. By binding to PD-1, Libtayo has been shown to block cancer cells from using the PD-1 pathway to suppress T-cell activation.

Libtayo is the first and only immunotherapy approved in the U.S., EU, and other countries for adults with metastatic cutaneous squamous cell carcinoma (CSCC) or locally advanced CSCC who are not candidates for curative surgery or curative radiation. In the U.S., the generic name for Libtayo in its approved indication 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.

The extensive clinical program for Libtayo is focused on difficult-to-treat cancers. In skin cancer, this includes a pivotal trial in advanced basal cell carcinoma and additional trials in adjuvant and neoadjuvant CSCC. Libtayo is also being investigated in pivotal Phase 3 trials in non-small cell lung cancer and cervical cancer, as well as in trials combining Libtayo with novel therapeutic approaches for both solid tumors and blood cancers. These potential uses – either as monotherapy or in combination with bispecifics – are investigational, and their safety and efficacy have not been evaluated by any regulatory authority.

Libtayo is being jointly developed by Regeneron and Sanofi under a global collaboration agreement. Libtayo was invented using Regeneron's proprietary *VelocImmune*® technology that utilizes a proprietary genetically-engineered mouse platform endowed with a genetically-humanized immune system to produce optimized fully-human antibodies. *VelocImmune* technology has been used to create multiple antibodies including Dupixent® (dupilumab), Praluent® (alirocumab) and Kevzara® (sarilumab), which are approved in multiple countries around the world. Regeneron previously used these technologies to rapidly develop a treatment for Ebola virus infection, which is currently under review by the FDA, and is now being used in efforts to create preventative and therapeutic medicines for COVID-19.

IMPORTANT SAFETY INFORMATION AND INDICATION FOR U.S. PATIENTS

What is Libtayo?
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.

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

What is the most important information I should know about Libtayo?
Libtayo is a medicine that may treat a type of skin cancer 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. 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 symptoms of the following problems or these symptoms get worse:

- **Lung problems (pneumonitis).** Signs and symptoms of pneumonitis may include new or worsening cough, shortness of breath, and chest pain.
- **Intestinal problems (colitis) that can lead to tears or holes in your intestine.** Signs and symptoms of colitis may include diarrhea (loose stools) or more frequent bowel movements than usual; stools that are black, tarry, sticky or that have blood or mucus; and severe stomach-area (abdomen) pain or tenderness.
- **Liver problems (hepatitis).** Signs and symptoms of hepatitis may include yellowing of your skin or the whites of your eyes, severe nausea or vomiting, pain on the right side of your stomach area (abdomen), drowsiness, dark urine (tea colored), bleeding or bruising more easily than normal, and feeling less hungry than usual.
- **Hormone gland problems** (especially the adrenal glands, pituitary, thyroid and pancreas). Signs and symptoms that your hormone glands are not working properly may include headaches that will not go away or unusual headaches, rapid heartbeat, increased sweating, extreme tiredness, weight gain or weight loss, dizziness or fainting, feeling more hungry or thirsty than usual, hair loss, feeling cold, constipation, deeper voice, very low blood pressure, urinating more often than

usual, nausea or vomiting, stomach-area (abdomen) pain, and changes in mood or behavior, such as decreased sex drive, irritability, or forgetfulness.

- **Kidney problems,** including nephritis and kidney failure. Signs of these problems may include decrease in your amount of urine, blood in your urine, swelling in your ankles, and loss of appetite.
- **Skin problems.** Signs of these problems may include rash, itching, skin blistering, and painful sores or ulcers in the mouth, nose, throat, or genital area.
- **Problems in other organs.** Signs of these problems may include headache, tiredness or weakness, sleepiness, changes in heartbeat (such as beating fast, seeming to skip a beat, or a pounding sensation), confusion, fever, muscle weakness, balance problems, nausea, vomiting, stiff neck, memory problems, seizures (encephalitis), swollen lymph nodes, rash or tender lumps on skin, cough, shortness of breath, vision changes, or eye pain (sarcoidosis), seeing or hearing things that are not there (hallucinations), severe muscle weakness, low red blood cells (anemia), bruises on the skin or bleeding, and changes in eyesight.
- **Rejection of a transplanted organ.** Your doctor should tell you what signs and symptoms you should report and monitor you, depending on the type of organ transplant that you have had.
- **Infusion (IV) reactions that can sometimes be severe and life-threatening.** Signs of these problems may include chills or shaking, itching or rash, flushing, shortness of breath or wheezing, dizziness, fever, feeling of passing out, back or neck pain, and facial swelling.

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 delay or completely stop treatment 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 had an organ transplant;
- have lung or breathing problems;
- have liver or kidney problems;
- have diabetes;
- 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 include tiredness, rash, and diarrhea. 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 and Sanofi at 1-877-542-8296.

For more information, please see full Prescribing Information, including Medication Guide.

About Regeneron Pharmaceuticals, Inc.
Regeneron (NASDAQ: REGN) is a leading biotechnology company that invents life-transforming medicines for people with serious diseases. Founded and led for over 30 years by physician-scientists, our unique ability to repeatedly and consistently translate science into medicine has led to seven FDA-approved treatments and numerous product candidates in development, 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, 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 additional information about the company, 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, 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 by Regeneron and/or its collaborators (collectively, "Regeneron's Products"), and the global economy; the nature, timing, and possible success and therapeutic applications of Regeneron's Products and Regeneron's product candidates and research and clinical programs now underway or planned, including without limitation Libtayo® (cemiplimab-rwlc), REGN5678 (a PSMAxCD28 costimulatory bispecific antibody being studied in combination with Libtayo), and Regeneron's other investigational bispecific antibodies discussed in this press release; uncertainty of market acceptance and commercial success of Regeneron's Products and product candidates and the impact of studies (whether conducted by Regeneron or others and whether mandated or voluntary) on the commercial success of Regeneron's Products and product candidates; 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 for the treatment of basal cell carcinoma, adjuvant and neoadjuvant cutaneous squamous cell carcinoma, non-small cell lung cancer, and cervical cancer (as well as in combination with novel therapeutic approaches for both solid tumors and blood cancers, as applicable); unforeseen safety issues resulting from the administration of Regeneron's Products (such as Libtayo) and product candidates (such as Regeneron's investigational bispecific antibodies discussed in this press release) in patients, including serious complications or side effects in connection with the use of Regeneron's Products and 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 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 Regeneron's Products and product candidates; the extent to which the results from the research and development programs conducted by Regeneron and/or its collaborators may 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, suppliers, or other third parties (as applicable) to perform manufacturing, filling, finishing, packaging, labeling, distribution, and other steps related to Regeneron's Products and 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, Bayer, and Teva Pharmaceutical Industries Ltd. (or their respective affiliated companies, as applicable), to be cancelled or terminated without any further product success; 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 Dupixent® (dupilumab) and Praluent® (alirocumab)), 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, 2019 and its Form 10-Q for the quarterly period ended March 31, 2020. 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 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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