First Clinical Data for REGN5458 (BCMAxCD3) Show Positive Preliminary Results in Multiple Myeloma

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TARRYTOWN, N.Y., Dec. 8, 2019 /PRNewswire/ -- Regeneron Pharmaceuticals, Inc. (NASDAQ: **REGN**) today announced initial clinical data for REGN5458, a BCMAxCD3 bispecific antibody, in patients with relapsed or refractory (R/R) multiple myeloma. BCMA (B-cell maturation antigen) is a protein that is typically over-expressed on multiple myeloma cells. REGN5458 is designed to bind to BCMA on multiple myeloma cells and the CD3 receptor on T-cells, bridging them together and activating T-cell killing of the cancer cell.

Results were presented today at the American Society of Hematology (ASH) Annual Meeting from the first two dose groups (3 mg and 6 mg weekly doses). Patients had a median of seven lines of prior systemic therapy, and all had failed CD38 antibody treatment. Responses were observed in 4 of 7 (57%) patients, including 3 of 4 (75%) in the 6 mg dose group. In the 6 mg dose group, 2 patients (50%) were also minimal residual disease (MRD) negative, meaning that no cancer cells were detectable in their bone marrow.

"We are encouraged to see promising, rapid clinical activity even at the initial two doses of REGN5458 in heavily pretreated patients with multiple myeloma. Two patients achieved the high bar of MRD negativity, and another patient attained a very good partial response despite entering the trial with difficult-to-treat plasmacytomas outside of the bone marrow," said Israel Lowy, M.D., Ph.D., Senior Vice President and Head of Clinical and Translational Sciences for Oncology at Regeneron. "We are actively recruiting patients into higher dose groups in this trial and look forward to sharing further results in 2020. In addition, we have also initiated a clinical trial for our second BCMAxCD3 bispecific, REGN5459, which has different binding characteristics."

REGN5458 and REGN5459 were invented using Regeneron's next generation *VelocImmune*® "human antibody mouse" technology, together with its *VelociBi* ™platform. These allow for the creation of bispecific antibodies that closely resemble natural human antibodies with no linkers or artificial sequences. Additionally, Regeneron bispecifics are manufactured using similar approaches used for human antibody medicines, with similar pharmacokinetics.

As of data cutoff, there have been no neurotoxicity, dose-limiting toxicities or treatment discontinuations due to adverse events (AEs). The most common treatment-emergent AEs were lymphopenia (n=5), anemia (n=4) and thrombocytopenia and cytokine release syndrome (n=3 each). Grade 3 or higher treatment-emergent AEs were seen in 5 patients and included lymphopenia (n=3), hypertension (n=2) and anemia, atrial fibrillation, fatigue, febrile neutropenia, pain in extremity, septic shock and thrombocytopenia (n=1 each).

Multiple myeloma is the second most common blood cancer, with approximately 32,000 and 138,500 new diagnoses in the U.S. and world respectively. It is characterized by the proliferation of cancerous plasma cells (multiple myeloma cells) that crowd out healthy blood cells in the bone marrow, infiltrate other tissues and cause potentially life-threatening organ injury. Recent advances, such as CD38 antibody treatment, have increased life expectancy of patients from 3-4 years to 7-8 years. Despite this, multiple myeloma remains incurable, and most patients will experience relapse and require additional therapy.

The REGN5458 data follow other positive results from Regeneron's growing bispecific pipeline, including updated REGN1979 data that will be presented at ASH. REGN1979 is an investigational CD3 bispecific that is being studied in R/R follicular lymphoma and diffuse large B-cell lymphoma, including in patients whose cancer did not respond to CAR-T therapy. Regeneron has also invented a second class of CD28 bispecifics, called co-stimulatory bispecifics, which have recently entered clinical trials.

About the REGN5458 Phase 1/2 Dose-escalation Trial
REGN5458 monotherapy is being investigated in an open-label, Phase 1/2 dose-escalation trial in patients with R/R multiple myeloma who have exhausted all therapeutic options, including proteasome inhibitors, immunomodulatory drugs and CD38 antibody treatments. The Phase 1 portion is assessing safety, tolerability and dose-limiting toxicities. Beyond the initial dose groups presented at ASH, additional dose groups are being evaluated to determine a recommended Phase 2 dose regimen. The Phase 2 portion will further assess REGN5458 anti-tumor activity and safety.

Among the patients being enrolled are those with heavily pre-treated multiple myeloma, including those with extra-medullary (outside of the bone marrow) and non-secretory disease (do not secrete detectable myeloma proteins).

In multiple myeloma clinical trials, treatment effectiveness is typically assessed by overall response rate (ORR; with response types categorized by the level of reduction in myeloma protein) and the rate of conversion to negative MRD (which measures the eradication of myeloma cells in bone marrow). For ORR, myeloma protein levels in the blood are reduced by more than 50% in partial responses (PR) and 90% in very good PR (VGPR), while complete responses are defined as no evidence of myeloma protein and ≤5% of plasma cells in the bone marrow. MRD is measured separately from ORR, and MRD negativity is defined as the absence of myeloma cells within 100,000 bone marrow cells.

About the Regeneron Bispecific Antibody Platform
All of Regeneron's bispecific antibodies are designed to closely resemble natural human antibodies. They are derived from a next-generation version of Regeneron's proprietary *VelocImmune* technology and created using the company's *VelociBi* platform.

There are six Regeneron investigational bispecific antibodies currently in ongoing clinical trials for multiple blood cancers and solid tumors. 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 (REGN1979) 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 PD-1 inhibitors and/or CD3 bispecifics. Investigational candidates include:

- PSMAxCD28 (REGN5678) in combination with Libtayo® (cemiplimab) for prostate cancer.

-- 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.

Regulatory Status of Oncology Programs
REGN1979, REGN5458, REGN5459, REGN4018, REGN5678, REGN5093 and Libtayo are currently under clinical development for the diseases noted in this press release, and their safety and efficacy have not been evaluated by any regulatory authority for these diseases. As part of a global collaboration agreement, Regeneron and Sanofi are jointly developing Libtayo, as well as Regeneron's BCMAxCD3 and MUC16xCD3 bispecific programs.

Libtayo is approved in the U.S. for the treatment of patients with metastatic cutaneous squamous cell carcinoma (CSCC) or locally advanced CSCC who are not candidates for curative surgery or curative radiation, and in other countries for similar indications. In the U.S., the generic name for Libtayo 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.

About Regeneron
Regeneron (NASDAQ: REGN) is a leading biotechnology company that invents life-transforming medicines for people with serious diseases. Founded and led for 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, infectious diseases, pain and rare diseases.

Regeneron is accelerating and improving the traditional drug development process through our proprietary *VelociSuite*® technologies, such as *VelocImmune*®, which uses a unique genetically-humanized mouse 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 nature, timing, and possible success and therapeutic applications of Regeneron's products, product candidates, and research and clinical programs now underway or planned, including without limitation REGN5458 (a BCMAxCD3 bispecific antibody) in patients with relapsed or refractory multiple myeloma, as well as REGN5459 (a BCMAxCD3 bispecific antibody), REGN1979 (a CD20xCD3 bispecific antibody), REGN4018 (a MUC16xCD3 bispecific antibody), REGN5678 (a PSMAxCD28 bispecific antibody), REGN5093 (a METxMET bispecific antibody), and Regeneron's earlier-stage product candidates (as a monotherapy or in combination with Libtayo® (cemiplimab), as applicable); unforeseen safety issues resulting from the administration of products and product candidates in patients, including serious complications or side effects in connection with the use of Regeneron's product candidates (such as REGN5458, REGN5459, REGN1979, REGN4018, REGN5678, and REGN5093) in clinical trials; the extent to which the results from the research and development programs conducted by Regeneron or its collaborators (including the open-label, Phase 1/2 dose-escalation trial evaluating REGN5458 discussed in this press release) may be replicated in other studies and lead to therapeutic applications; the likelihood, timing, and scope of possible regulatory approval and commercial launch of Regeneron's late-stage product candidates and new indications for marketed products; ongoing regulatory obligations and oversight impacting Regeneron's marketed products, research and clinical programs, and business, including those relating to patient privacy; 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; competing drugs and product candidates that may be superior to Regeneron's products and product candidates; 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 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; the availability and extent of reimbursement of the Company'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; 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 fiscal year ended December 31, 2018 and its Form 10-Q for the quarterly period ended September 30, 2019. 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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