REGENERON

Publication Highlights Regeneron's Costimulatory Bispecific Antibodies, an Emerging Class of Cancer Immunotherapy

January 8, 2020

TARRYTOWN, N.Y., Jan. 8, 2020 /PRNewswire/ --

Preclinical results published in _Science Translational Medicine_ show that adding CD28 costimulatory bispecifics to CD3 bispecifics led to synergistic anti-tumor activity without inducing cytokine storm

First costimulatory bispecific clinical trial initiated for prostate cancer; multiple additional costimulatory bispecifics to enter the clinic this year

Regeneron Pharmaceuticals, Inc. (NASDAQ: **REGN**) today announced a publication featured on the cover of _Science Translational Medicine_ describing the potential of a new class of cancer immunotherapy known as "costimulatory bispecific antibodies." Regeneron and others have previously shown that CD3 bispecifics can result in meaningful clinical responses in previously untreatable cancer settings. The results published today show that adding a novel class of CD28 costimulatory bispecifics to Regeneron's CD3 bispecifics can lead to synergistic anti-tumor activity in multiple cell culture and animal model experiments, without inducing systemic cytokine release (cytokine storm).

"This novel class of CD28 costimulatory bispecifics are key to our strategy of developing a broad oncology portfolio – based on rational combinations to efficiently engage the immune system – to address a broad range of cancers, including those that are not responsive to currently available immunotherapy," said George D. Yancopoulos, M.D., Ph.D., Co-Founder, President and Chief Scientific Officer at Regeneron. "We have dosed prostate cancer patients with our first CD28 costimulatory bispecific, REGN5678, in combination with Libtayo® (cemiplimab), and we plan to advance additional CD28 costimulatory bispecifics into the clinic for other cancers this year, including in combinations with CD3 bispecifics."

The rationale for combining CD3 and CD28 bispecific antibodies is based on the fact that T-cells require two signals to fully activate. The first "recognition" signal occurs when the T-cell identifies a foreign or mutated protein (antigen), via its T-cell receptor/CD3 complex. However, the T-cell is only fully activated for cancer cell killing after it receives a second "costimulatory" signal, most powerfully via the CD28 costimulatory receptor. Regeneron's CD3 and CD28 investigational bispecifics are designed to bridge T-cells to cancer cells and simultaneously provide activation through these two signals. The publication demonstrates that this combination approach can drive markedly enhanced T-cell killing of prostate and ovarian tumors in sophisticated genetically-humanized animal models.

"Cancer researchers have long known that CD28-targeted therapies have the ability to supercharge T-cells against cancer, but little progress was made in harnessing this powerful opportunity given historic safety findings with CD28 superagonists. Our goal was to engage the CD28 pathway in a completely novel and targeted way to avoid the issues with generalized CD28 activation," said Dimitris Skokos, Ph.D., Senior Director, Cancer Immunology Research at Regeneron. "Costimulatory bispecifics offered an innovative solution that allowed us to design antibodies with molecular controls to use CD28 to boost T-cell activation only in the presence of cancer cells and after the 'recognition' signal had been received. To see this design work preclinically is gratifying, and we are excited to see if these results will translate in human clinical trials."

CD28 superagonists were investigational CD28-targeted monoclonal antibodies. In a Phase 1 trial conducted in 2006 by another company, a CD28 superagonist overactivated T-cells throughout the bodies of healthy volunteers. This caused life-threatening levels of cytokine release syndrome (known as cytokine storm), leading to multiple organ failure. As a result, clinical research into CD28-based treatments was largely stopped.

This led Regeneron to carefully select CD28 costimulatory bispecific antibody candidates that would only activate T-cells when they were bridged to cancer cells and after having received the first "recognition" signal. Regeneron also tested the safety of its CD28 costimulatory bispecifics in several animal models and showed they did not induce cytokine storm when administered as monotherapy or in combination. These findings support the further investigation of CD28 costimulatory bispecifics in combination with other treatments.

"Checkpoint inhibitors and CAR-T cell therapy have transformed cancer treatment over the past decade, but many patients still don't respond to these immunotherapies. That's why it's exciting to see Regeneron's CD28 costimulatory bispecifics emerge as promising future off-the-shelf solutions," said Jill O'Donnell-Tormey, Ph.D., Chief Executive Officer and Director of Scientific Affairs at the Cancer Research Institute. "The data published in _Science Translational Medicine_ show that Regeneron is helping to expand the boundaries of what may be possible with immunotherapy."

Among the investigational medicines studied in the paper were two CD28 costimulatory bispecifics (PSMAxCD28 and MUC16xCD28) and two CD3 bispecifics (CD20xCD3 and MUC16xCD3).

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 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 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
The bispecifics mentioned in this release are currently under clinical development, and their safety and efficacy have not been evaluated by any regulatory authority.

Libtayo in combination with REGN5678 is currently under clinical development for prostate cancer, and its safety and efficacy have not been evaluated by any regulatory authority for this use. Libtayo is currently 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.

As part of a global collaboration agreement, Regeneron and Sanofi are jointly developing Libtayo, as well as Regeneron's BCMAxCD3 and MUC16xCD3 bispecific programs.

About Regeneron
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, 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 REGN5678 (a PSMAxCD28 costimulatory bispecific antibody) being studied in combination with Libtayo® (cemiplimab) for the treatment of prostate cancer, as well as REGN1979 (a CD20xCD3 bispecific antibody), REGN5458 (a BCMAxCD3 bispecific antibody), REGN5459 (a BCMAxCD3 bispecific antibody), REGN4018 (a MUC16xCD3 bispecific antibody), REGN5093 (a METxMET bispecific antibody), and Regeneron's earlier-stage product candidates (such as Regeneron's other costimulatory bispecific antibodies discussed in this press release); 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 Regeneron's bispecific antibodies and costimulatory bispecific antibodies discussed in this press release) in clinical trials; the likelihood and timing of achieving any anticipated development milestones discussed or referenced in this press release; the extent to which the results from the research and development programs conducted by Regeneron or its collaborators 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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