

REGENERON

Novel Costimulatory Bispecific Antibody Shows Encouraging Anti-tumor Activity When Combined with PD-1 Inhibitor Libtayo® (cemiplimab) in Advanced Metastatic Castration-resistant Prostate Cancer (mCRPC)

August 3, 2022

First clinical data from ongoing Phase 1/2 trial show dose-dependent anti-tumor activity for investigational REGN5678 (PSMAxCD28) when combined with standard dose Libtayo, suggesting potential to overcome mCRPC resistance to PD-1 inhibition

Anti-tumor activity correlated with immune-related adverse events

These data provide early evidence and proof of principle for Regeneron's broader costimulatory bispecific platform, which includes three CD28 bispecifics in ongoing clinical trials and additional candidates in preclinical development

TARRYTOWN, N.Y., Aug. 3, 2022 /PRNewswire/ -- Regeneron Pharmaceuticals, Inc. (NASDAQ: REGN) today announced encouraging initial data from an ongoing Phase 1/2 trial investigating REGN5678, a novel PSMAxCD28 costimulatory bispecific antibody, in combination with the company's PD-1 inhibitor Libtayo® (cemiplimab) in advanced metastatic castration-resistant prostate cancer (mCRPC). REGN5678 is one of Regeneron's three clinical-stage costimulatory bispecifics, all of which are designed to bridge T cells to cancer cells and augment CD28 signaling to increase anti-tumor activity in combination with Libtayo or a CD3 bispecific.

"In past clinical trials, metastatic castration-resistant prostate cancer has been largely unresponsive to PD-1 inhibition and immunotherapy in general, leaving patients with inadequate treatment options, a poor prognosis and an expected survival of one to two years depending on the treatment history," said Mark Stein, M.D., a trial investigator and Associate Professor of Medical Oncology at Columbia University Vagelos College of Physicians and Surgeons. "These initial data provide the first clinical evidence indicating that a costimulatory bispecific antibody may synergistically combine with an anti-PD-1 agent such as Libtayo to enable activity against a tumor class previously resistant to anti-PD-1 immunotherapy. We look forward to further investigating the safety and efficacy of this combination."

The Phase 1/2, first-in-human, open label trial is currently enrolling patients with advanced mCRPC whose tumors have previously progressed on multiple anti-androgen therapies, with a majority also having received prior chemotherapy. In the Phase 1 dose-escalation portion, patients are initiated with weekly doses of REGN5678, for three weeks, to assess the safety and efficacy of this novel costimulatory antibody alone, which then continues in combination with standard dose Libtayo. The primary endpoints are safety, tolerability and pharmacokinetics. The key secondary endpoint is objective response rate defined as a $\geq 50\%$ decline of prostate-specific antigen (PSA) from baseline and/or tumor shrinkage. PSA is a protein produced by the prostate gland and is commonly used as a biomarker to diagnose and follow prostate cancer, as many mCRPC patients have disease limited to bone lesions and cannot be assessed by conventional RECIST 1.1 criteria.

Preliminary data from the ongoing dose-escalation portion of the trial, across 8 dose level cohorts and a total of 33 patients, showed dose-dependent anti-tumor activity per centrally collected PSA values, as well as investigator reports. Not all patients have undergone or completed tumor assessments and the data are not yet final. At the lowest dose levels (cohorts 1-5), there was almost no evidence of anti-tumor activity, with only 1 of 17 patients showing a decrease (22%) in PSA; there were no \geq grade (Gr) 3 immune-related adverse events (irAE) at these doses. The lack of anti-tumor activity among these patients was consistent with the approximate 6% response rate reported in other trials with anti-PD1 monotherapy.

At the next three dose levels (cohorts 6-8), evidence of dose-dependent anti-tumor activity was generally seen within 6 weeks of starting combination treatment as follows:

- **Cohort 6:** 1 of 4 patients experienced a 100% decrease in PSA and a complete response (CR) in target lesions based on RECIST 1.1 criteria. The patient discontinued therapy due to a Gr3 irAE of the skin (that was considered to be a recurrence of a pre-existing condition, and has resolved with treatment per investigator report). The patient has maintained the 100% decrease in PSA and CR in target lesions for approximately 10 months to date per investigator report.
- **Cohort 7:** 3 of 8 patients experienced decreases in PSA of >99%, 44% and 22%. Two of these three patients had a Gr3 AE (aseptic encephalitis and seizure, respectively, both of which have resolved).
- **Cohort 8:** 3 of 4 patients experienced decreases in PSA of >99%, >99% and 82%. Of the two patients with >99% PSA reductions, one experienced a Gr3 case of mucositis (resolved) and the other experienced a Gr3 case of acute inflammatory demyelinating polyradiculopathy (ongoing).

In terms of safety, no \geq Gr3 irAEs were observed in patients without anti-tumor activity, and the occurrence of irAEs was correlated with anti-tumor activity; this is consistent with previous trials with anti-PD-1 immunotherapy, wherein irAEs have been reported to occur at a higher rate in responding patients. No Gr4 irAEs or \geq Gr2 cytokine release syndrome have been observed in the trial to date. There was one death that was considered unrelated to treatment. In this trial, irAEs are being treated according to standard management practices used for checkpoint inhibitors.

Additional data are planned for presentation at an upcoming medical meeting.

"Through extensive [preclinical research](#), we hypothesized that augmenting T-cell costimulation alongside PD-1 inhibition could be a key to turning immunologically 'cold' tumors 'hot,'" said George D. Yancopoulos, M.D., Ph.D., President and Chief Scientific Officer at Regeneron. "These preliminary data for our PSMAxCD28 costimulatory bispecific provide the first clinical evidence supporting the promise of our broader pipeline of costimulatory

bispecifics in diverse solid tumors and hematological malignancies. By combining these costimulatory bispecifics with Libtayo or our CD3 bispecifics, we have the opportunity to create novel therapeutic synergies to address some of the most difficult-to-treat cancers. We look forward to partnering with the oncology community on this ambitious and potentially groundbreaking research."

The combination of REGN5678 and Libtayo is currently under clinical development for mCRPC, and its safety and efficacy have not been fully evaluated by any regulatory authority.

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 limitation Libtayo[®] (cemiplimab-rwlc), REGN5678 (a PSMAxCD28 costimulatory bispecific antibody being studied in combination with Libtayo), and Regeneron's other investigational bispecific antibodies discussed or referenced in this press release; uncertainty of 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) on the commercial success of Regeneron's Products and Regeneron's 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 REGN5678 in combination with Libtayo for the treatment of metastatic castration-resistant prostate cancer; safety issues resulting from the administration of Regeneron's Products (such as Libtayo) and Regeneron's Product Candidates (such as REGN5678 and Regeneron's other 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 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 (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, 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, Bayer, and Teva Pharmaceutical Industries Ltd. (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[®] (afibercept) Injection, 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, 2021 and its Form 10-Q for the quarterly period ended June 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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