New Data Presented at European Society for Medical Oncology Meeting Demonstrate Antitumor Activity with IONIS-STAT3-2.5 Rx in Combination with Imfinzi

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29% Objective Response Rate and 57% Disease Control Rate in Combination with Immune Checkpoint Inhibitor Treatment in Patients with Head and Neck Cancer

Four Complete Responses and Four Partial Responses Observed in 28-patient Study

CARLSBAD, Calif., Sept. 11, 2017 /PRNewswire/ -- Ionis Pharmaceuticals, Inc. (NASDAQ: IONS) today reported that new data from the clinical program for IONIS-STAT3-2.5$_{Rx}$ (AZD9150) were presented at the 2017 European Society for Medical Oncology (ESMO) Annual Congress. The presentation included clinical and safety results from the Phase 1b/2 study evaluating the activity of IONIS-STAT3-2.5$_{Rx}$ in combination with Imfinzi (durvalumab), AstraZeneca's programmed death ligand (PD-L1) blocking antibody, in patients with advanced solid tumors and recurrent metastatic head and neck cancer. In the study, the combination treatment resulted in encouraging antitumor activity with a safety and tolerability profile supportive of continued development.

"Today's positive data with IONIS-STAT3-2.5$_{Rx}$ are exciting, demonstrating robust activity that is comparable to other promising late-stage checkpoint inhibitor combination therapies for cancer. We continue to be encouraged by the substantial antitumor activity of our Generation 2.5 antisense drugs. Our Generation 2.5 chemistry increases the potency of our antisense drugs, thereby creating opportunities for drugs like IONIS-STAT3-2.5$_{Rx}$ to be effective in targeting more diseases with high unmet need, such as cancers," said Brett Monia, Ph.D., senior vice president of drug discovery and franchise leader for oncology and rare diseases at Ionis Pharmaceuticals. "We are enthusiastic about the broad clinical program AstraZeneca is conducting to evaluate the potential of combining our antisense drugs with immunotherapy approaches to deliver potent and targeted treatment options to patients stricken with various cancers."

"We are encouraged by the anti-tumor activity and safety profile observed in patients with head and neck cancer with AZD9150 in combination with Imfinzi," said Susan Galbraith. M.B., B.Chir., Ph.D. senior vice president and head of oncology innovative medicines unit at AstraZeneca. "We believe this combination therapy supports further study in this group as well as patients with other cancers."

Results from the study were presented at the 2017 ESMO Annual Congress in an oral presentation titled, "Phase 1b/2 Study (SCORES) Assessing Safety, Tolerability, and Preliminary Anti-tumor Activity of Durvalumab Plus AZD9150 or AZD5069 in Patients With Advanced Solid Tumors and Refractory and Metastatic (R/M) Squamous Cell Carcinoma of the Head and Neck (R/M-SCCHN)." In the study, combination therapy with IONIS-STAT3-2.5$_{Rx}$ and Imfinzi in 28 PD-L1 treatment naïve patients with R/M-SCCHN resulted in encouraging antitumor activity and deep responses to treatment. The treatment combination demonstrated a 29% (8/28) objective response rate with four partial responses (PR) and four complete responses (CR), of which one was a CR in target lesions only. An additional eight patients on the treatment combination had stable disease (SD) at 12 weeks, resulting in an overall disease control rate of 57% (16/28). Importantly, a complete response was seen in a patient with R/M-SCCHN that was refractory to previous PD-L1 treatment. Combination therapy with IONIS-STAT3-2.5$_{Rx}$ and Imfinzi demonstrated a manageable safety profile. The most common drug-related adverse events occurred infrequently and were similar to those observed with other drugs targeting the JAK/STAT pathway, including mild liver enzyme increases, mild platelet count decreases and mild anemia.

The Phase 1b/2 study is currently ongoing and enrolling an additional treatment group. AstraZeneca is also currently evaluating IONIS-STAT3-2.5$_{Rx}$ in combination with Imfinzi in patients with diffuse large B cell lymphoma.

About IONIS-STAT3-2.5$_{Rx}$

IONIS-STAT3-2.5$_{Rx}$, also referred to as AZD9150, is a Generation 2.5 antisense drug designed to reduce the production of signal transducer and activator of transcription 3, or STAT3, for the treatment of patients with cancer. STAT3 is a protein involved in the translation of key factors critical for tumor cell growth and survival and is an important factor in immune cells of the tumor microenvironment where it contributes to the ability of tumors to evade the host immune system. STAT3 is over-active in a variety of cancers, including brain, lung, breast, bone, liver and multiple myeloma.

Ionis licensed IONIS-STAT3-2.5$_{Rx}$ to AstraZeneca for the treatment of cancer. AstraZeneca is currently evaluating IONIS-STAT3-2.5$_{Rx}$ in combination with Imfinzi, AstraZeneca's programmed death ligand (PDL1) blocking antibody, in multiple Phase 2 studies, including in patients with head and neck cancer in patients with diffuse large B cell lymphoma.

ABOUT IONIS PHARMACEUTICALS, INC.

Ionis is the leading company in RNA-targeted drug discovery and development focused on developing drugs for patients who have the highest unmet medical needs, such as those patients with severe and rare diseases. Using its proprietary antisense technology, Ionis has created a large pipeline of first-in-class or best-in-class drugs, with over three dozen drugs in development. SPINRAZA® (nusinersen) has been approved in the U.S., Europe, Japan, Canada and Brazil for the treatment of spinal muscular atrophy (SMA). Biogen is responsible for commercializing SPINRAZA. Drugs that have successfully completed Phase 3 studies include inotersen (IONIS-TTR$_{Rx}$), an antisense drug Ionis is developing to treat patients with TTR amyloidosis, and volanesorsen, an antisense drug discovered by Ionis and co-developed by Ionis and Akcea Therapeutics to treat patients with either familial chylomicronemia syndrome or familial partial lipodystrophy. Akcea, an affiliate of Ionis, is a biopharmaceutical company focused on

developing and commercializing drugs to treat patients with serious cardiometabolic diseases caused by lipid disorders. If approved, volanesorsen will be commercialized through Ionis' affiliate, Akcea. Both inotersen and volanesorsen are progressing toward regulatory filings for marketing authorization. Ionis' patents provide strong and extensive protection for its drugs and technology. Additional information about Ionis is available at www.ionispharma.com.

IONIS' FORWARD-LOOKING STATEMENT

This press release includes forward-looking statements regarding Ionis' alliance with AstraZeneca and the therapeutic and commercial potential of IONIS-STAT3-2.5$_{Rx}$. Any statement describing Ionis' goals, expectations, financial or other projections, intentions or beliefs is a forward-looking statement and should be considered an at-risk statement. Such statements are subject to certain risks and uncertainties, particularly those inherent in the process of discovering, developing and commercializing drugs that are safe and effective for use as human therapeutics, and in the endeavor of building a business around such drugs. Ionis' forward-looking statements also involve assumptions that, if they never materialize or prove correct, could cause its results to differ materially from those expressed or implied by such forward-looking statements. Although Ionis' forward-looking statements reflect the good faith judgment of its management, these statements are based only on facts and factors currently known by Ionis. As a result, you are cautioned not to rely on these forward-looking statements. These and other risks concerning Ionis' programs are described in additional detail in Ionis' annual report on Form 10-K for the year ended December 31, 2016, and its most recent quarterly report on Form 10-Q, which are on file with the SEC. Copies of these and other documents are available from the Company.

In this press release, unless the context requires otherwise, "Ionis," "Company," "we," "our," and "us" refers to Ionis Pharmaceuticals and its subsidiaries.

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SOURCE Ionis Pharmaceuticals, Inc.

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