ISIS-STAT3 Rx and ISIS-AR Rx Data Presented by AstraZeneca at European Cancer Symposium

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CARLSBAD, Calif., Nov. 20, 2014 /PRNewswire/ -- Isis Pharmaceuticals, Inc. (NASDAQ: ISIS) announced today that data from two drugs in its anti-cancer franchise will be presented by researchers at AstraZeneca in three presentations at the 26th European Organization for Research and Treatment of Cancer (EORTC) – the National Cancer Institute (NCI) – and the American Association for Cancer Research (AACR) symposium. Results from a Phase 1/2 clinical study presented today provided preliminary evidence of antitumor activity for ISIS-STAT3$_{Rx}$ (AZD9150) in patients with cancer including advanced/metastatic hepatocellular carcinoma (HCC). This adds to previous data for ISIS-STAT3$_{Rx}$ showing evidence of antitumor activity in other cancer types, including diffuse large B cell lymphoma. Additional data to be presented at the conference demonstrate that ISIS-STAT3$_{Rx}$ reduced STAT3 levels in multiple cell types relevant to cancer growth and survival, clinically and pre-clinically. Based on these findings, as well as very encouraging preclinical data in animal models of cancer, AstraZeneca plans to evaluate ISIS-STAT3$_{Rx}$ as an immunomodulatory agent in combination with MEDI4736, AstraZeneca's investigational anti-PD-L1 immune checkpoint inhibitor. In addition, AstraZeneca will also present preclinical data on ISIS-AR$_{Rx}$ (AZD5312) showing that the drug is active in several tumor models.

"Based on the data from the initial trials we are excited about the potential for STAT3 inhibition in the tumor microenvironment combined with immune checkpoint inhibition. Clinical studies are expected to initiate in the first half of 2015," said Susan Galbraith, Head of Oncology Innovative Medicines Unit, AstraZeneca.

"AstraZeneca's expertise and development capabilities to develop anti-cancer drugs have significantly enhanced the development of ISIS-STAT3$_{Rx}$ and ISIS-AR$_{Rx}$. Both of these drugs have demonstrated substantial antitumor activity in preclinical studies. We are encouraged with the anti-cancer activity observed with ISIS-STAT3$_{Rx}$ treatment in clinical studies, in which we've observed durable responses in patients with advanced lymphoma and also in patients with metastatic liver cancer," said Brett Monia, Ph.D., senior vice president of Antisense Drug Discovery at Isis Pharmaceuticals. "In addition, we are encouraged with the progress of ISIS-AR$_{Rx}$ and look forward to the results from the ongoing ISIS-AR$_{Rx}$ clinical study in patients with cancer."

Isis and AstraZeneca are collaborating on the development of ISIS-STAT3$_{Rx}$ and ISIS-AR$_{Rx}$ for the treatment of patients with cancer. At EORTC-NCI-AACR researchers will present data on both ISIS-STAT3$_{Rx}$ and ISIS-AR$_{Rx}$, including:

- Clinical data from ISIS-STAT3$_{Rx}$, which were presented in an oral presentation titled, 'Results of a Phase 1, open-label, muticentre study to assess the safety, tolerability, pharmacokinetics and preliminary antitumor activity of AZD9150 in patients with advanced/metastatic hepatocellular carcinoma' on Thursday, Nov. 20. In this presentation, treatment with ISIS-STAT3$_{Rx}$ provided evidence of antitumor activity in patients with HCC. In this late-stage population, several patients experienced stable disease and one patient experienced a durable, partial response (78% tumor shrinkage) while on ISIS-STAT3$_{Rx}$ treatment.
- Preclinical data from ISIS-STAT3$_{Rx}$, which will be presented in a poster titled, 'Immunological STAT3 knockdown associated with antitumor activity in preclinical models translates to clinical samples, suggesting immune modulation contributes to the clinical activity of AZD9150, a therapeutic STAT3 ASO' on Friday, Nov. 21. Preclinical and clinical data from this presentation show that ISIS-STAT3$_{Rx}$ is distributed to tumor, stromal and immune cells and are consistent with reduction of STAT3 in these cells contributing to antitumor activity.
- Preclinical data from ISIS-AR$_{Rx}$, which will be presented in a poster titled, 'Preclinical pharmacology of ISIS 560131, a generation 2.5 antisense oligonucleotide targeting the androgen receptor with differentiated activity from enzalutamide' on Friday, Nov. 21. Preclinical data from this presentation shows that ISIS-AR$_{Rx}$ can substantially reduce levels of all forms of the androgen receptor, including splice variants that have been implicated in promoting androgen resistance in prostate cancer. Moreover, evidence was presented demonstrating that ISIS-AR$_{Rx}$ is effective in prostate cancer models that display resistance to current standard of care prostate cancer treatments.

Isis Pharmaceuticals and AstraZeneca entered into a collaboration, development and license agreement in 2012 in oncology, subsequently expanded in 2013 to include CVMD. Under the 2012 agreement, one of the molecules being developed is ISIS-STAT3$_{Rx}$, a first-in-human, first-in-class, generation 2.5 antisense oligonucleotide inhibitor of STAT3, which is being developed as an immunomodulatory agent in combination with MEDI4736, AstraZeneca's investigational anti-PD-L1 immune checkpoint inhibitor. A second product of that collaboration, a generation 2.5 antisense drug targeting the androgen receptor, ISIS-AR$_{Rx}$, is in a Phase 1/2 study. This month, Isis and AstraZeneca expanded their relationship by entering into a collaboration to develop novel delivery methods for antisense oligonucleotides. This new collaboration builds on the existing relationship and could also bring benefits to these programs.

About ISIS-STAT3$_{Rx}$

ISIS-STAT3$_{Rx}$ is a generation 2.5 antisense drug designed to specifically reduce the production of signal transducer and activator of transcription 3 (STAT3). STAT3 is a gene that blocks natural cell death and is critical for tumor cell growth and survival. Inhibition of STAT3 has been shown to block the induction of tumor-associated cytokines involved in the progression of cancer, such as IL-6, IL-1, TGFb, and IL-10, which could serve as important biomarkers in clinical studies. Isis and AstraZeneca are currently evaluating ISIS-STAT3$_{Rx}$ in two clinical studies in patients with HCC and advanced lymphomas. Because STAT3 is overexpressed in numerous types of cancers, ISIS-STAT3$_{Rx}$ has the potential to be broadly useful for both solid and hematological tumors.

About ISIS-AR$_{Rx}$

ISIS-AR$_{Rx}$ is a generation 2.5 antisense drug designed to inhibit the production of AR for the treatment of patients with prostate cancer. Prostate cancer growth, proliferation and progression are all androgen-dependent, and AR function is involved in disease progression at all stages of prostate cancer. For patients diagnosed with metastatic prostate cancer, current treatments largely involve opposing the action of androgens by blocking the androgen receptor or removing circulating androgens. Although androgen deprivation therapy approaches are initially effective in delaying disease progression in patients with metastatic prostate cancer, over time the course of the disease will progress in many of these patients. Resistance to current therapies is frequent and can occur through a variety of mechanisms including the activation of AR signaling in tumor cells through the amplification, overexpression and mutation of the AR gene. Because ISIS-AR$_{Rx}$ can inhibit the production of all known forms of AR, including variants of the AR gene, this drug has the potential to be an effective treatment for all stages of prostate cancer, including prostate cancer patients who are resistant to current therapies.

ABOUT ISIS PHARMACEUTICALS, INC.

Isis is exploiting its leadership position in antisense technology to discover and develop novel drugs for its product pipeline and for its partners. Isis' broad pipeline consists of 34 drugs to treat a wide variety of diseases with an emphasis on cardiovascular, metabolic, severe and rare diseases, including neurological disorders, and cancer. Isis' partner, Genzyme, is commercializing Isis' lead product, KYNAMRO®, in the United States and other countries for the treatment of patients with homozygous FH. Isis has numerous drugs in Phase 3 development in severe and rare and cardiovascular diseases. These include a novel triglyceride lowering drug, ISIS-APOCIII$_{Rx}$, for patients with familial chylomicronemia syndrome; ISIS-TTR$_{Rx}$, which Isis is developing with GSK to treat patients with the polyneuropathy form of TTR amyloidosis; and, ISIS-SMN$_{Rx}$, which Isis is developing with Biogen Idec to treat infants and children with spinal muscular atrophy, a severe and rare neuromuscular disease. Isis' patents provide strong and extensive protection for its drugs and technology. Additional information about Isis is available at www.isispharm.com.

ISIS PHARMACEUTICALS' FORWARD-LOOKING STATEMENT

This press release includes forward-looking statements regarding Isis' collaboration with AstraZeneca and the discovery, development, activity, therapeutic potential, safety and commercialization of antisense drugs, including ISIS-STAT3$_{Rx}$ and ISIS-AR$_{Rx}$, arising from the collaboration. Any statement describing Isis' 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. Isis' 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 Isis' forward-looking statements reflect the good faith judgment of its management, these statements are based only on facts and factors currently known by Isis. As a result, you are cautioned not to rely on these forward-looking statements. These and other risks concerning Isis' programs are described in additional detail in Isis' annual report on Form 10-K for the year ended December 31, 2013, 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, "Isis," "Company," "we," "our," and "us" refers to Isis Pharmaceuticals and its subsidiaries.

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