Clay B. Siegall, Ph.D., President, CEO and Chairman of the Board at Seattle Genetics, Inc. recently gave the opening keynote presentation at CHI’s 5th Annual Antibody-Drug Conjugates Conference at the PEGS Summit in Boston. Below he shared his experience and perspective of what the future holds for ADCs and Seattle Genetics, Inc.

Seattle Genetics’ ADCETRIS® is the first in a new class of ADCs. What is the next step for Seattle Genetics in the field of ADCs?

We are proud that ADCETRIS® (brentuximab vedotin) has been used to treat more than 15,000 lymphoma patients globally to-date, and believe that it has the opportunity to be the foundation of therapy for CD30-expressing malignancies. Our most important near-term milestone for this program is a decision from the FDA regarding our supplemental Biologics License Application (BLA) for ADCETRIS in the AETHERA setting for the post-transplant consolidation treatment of Hodgkin lymphoma (HL) patients at high risk of relapse or progression. An estimated 50 percent of HL patients who undergo an autologous stem cell transplant are at risk of relapse and there have been few therapeutic advances that improve patient outcomes. We are encouraged by the strong clinical package that we submitted to the FDA, and we are looking forward to a decision from the FDA regarding our supplemental BLA by August 18th of this year. In addition, we have three other phase 3 clinical trials that are ongoing, called ALCANZA, ECHELON-1 and ECHELON-2. ALCANZA is a randomized trial of ADCETRIS versus standard of care for relapsed cutaneous T-cell lymphoma. We expect to complete enrollment to ALCANZA this year and report data in 2016, representing our next potential label expansion for ADCETRIS. With the ECHELON trials, our goal is to redefine the way frontline HL and mature T-cell lymphoma patients are treated by adding ADCETRIS into the standard regimens while dropping the most toxic agents. We expect to complete enrollment to ECHELON-1 later this year and to ECHELON-2 next year, with data readouts for both trials expected in the 2017 to 2018 timeframe.

Beyond ADCETRIS, we are advancing seven clinical-stage programs. Our lead ADC programs include SGN-CD33A in acute myeloid leukemia and SGN-CD19A in non-Hodgkin lymphoma, which have generated encouraging data that have led to expanded clinical programs. We plan to report additional data from these programs in the second half of 2015. More broadly, across the industry, we have collaborations with a dozen leading biotechnology and pharmaceutical companies and our technology empowers more than 20 of the ADCs in clinical development through both our proprietary and collaborator programs.

Where do you see the field of ADCs moving towards? What are some of the hurdles and challenges that the industry still needs to overcome to bring more ADCs to the market?

Critical considerations in ADC development include an internalizing antibody targeted to a highly specific tumor antigen, a potent synthetic drug and a stable linker enabling intratumoral release of the drug. With ADCETRIS, we combine key aspects of all three of these elements of a successful ADC. We continue to leverage the experience gained from bringing ADCETRIS to market in 2011 and build upon our significant research in ADC technology to drive innovation in the field of ADCs. For example, at the American Association for Cancer Research (AACR) Annual Meeting last month, we presented data on novel technologies that we are utilizing in our pipeline programs, including new antibody, linker and cytotoxic payload components and drug designs.

As the industry continues to gain experience with immuno-oncology compounds, I believe that there is an opportunity to bring these two types of targeted approaches together to provide greater activity. At Seattle
Genetics, we recently presented data at the AACR Annual Meeting on immunogenic cell death caused by ADCETRIS in vitro, providing further rationale for two planned clinical trials in combination with nivolumab under our recently announced collaboration with Bristol Myers Squibb. Combinations of these novel modalities are the future of treatment in oncology and we’re excited to be an integral part of the industry.

**At the ADCs: Preclinical and Clinical Updates conference, you delivered a Keynote Address on “ADCs: Building on the Past, Delivering on the Present and Optimizing for the Future”. Can you give us an overview of your talk and what you shared with us?**

As the industry leader in developing ADCs, I spoke about Seattle Genetics’ experience in the development of ADCs over the past 17 years. I reviewed our early experience with ADC technology and what led to the development of our first commercial product, ADCETRIS. Next, I discussed where we are as a company in delivering on the significant research that we have implemented since our founding and the company’s current great trajectory. Lastly, I reviewed the integral role ADCs play in the treatment of cancer and my view on the future of treatment in oncology.

**Beyond ADCETRIS, what are you most excited about in Seattle Genetics’ development pipeline?**

We’ve made significant investments in our product pipeline and I’m particularly excited about our two lead pipeline programs, SGN-CD33A and SGN-CD19A.

SGN-CD33A is a new ADC that we’ve developed targeting CD33 which is expressed on most acute myeloid leukemia cells irrespective of type. There is a significant need for new treatments in acute myeloid leukemia as overall survival has not meaningfully changed in the past three decades. SGN-CD33A is comprised of three parts: a cysteine-engineered anti-CD33 antibody enabling uniform site-specific conjugation, a cleavable dipeptide linker that is highly stable in circulation, and a pyrrolobenzodiazepine (PBD) dimer that binds DNA with high intrinsic affinity. PBD dimers are a class of DNA-crosslinking agents significantly more potent than systemic chemotherapeutic drugs. We have selected and optimized specific PBD molecules for our proprietary use in ADCs. In addition, SGN-CD33A employs a novel linker system and proprietary, site-specific conjugation technology (EC-mAb) that allows uniform drug-loading of the cell-killing PBD dimer to the anti-CD33 antibody. The ADC is designed to be stable in the bloodstream and to release its cytotoxic agent upon internalization into CD33-expressing cells.

We’ve reported promising early data from our ongoing SGN-CD33A phase 1 study, which we presented at the American Society of Hematology Annual Meeting last December. We’re looking forward to presenting additional data set from the phase 1 trials this year.

SGN-CD19A is an ADC targeting CD19, a protein expressed broadly on B-cell malignancies. SGN-CD19A is comprised of an anti-CD19 monoclonal antibody linked to a synthetic cell-killing agent, monomethyl auristatin F (MMAF). The ADC is designed to be stable in the bloodstream, and to release its cytotoxic agent upon internalization into CD19-expressing tumor cells. This approach is intended to spare non-targeted cells and thus reduce many of the toxic effects of traditional chemotherapy while enhancing the antitumor activity.

We’ve reported encouraging phase 1 data from an ongoing SGN-CD19A clinical trial in non-Hodgkin lymphoma and are particularly encouraged by data in relapsed diffuse large B-cell lymphoma (DLBCL) patients, where we saw a single-agent response rate of 55 percent. We plan to initiate a randomized phase 2 trial evaluating SGN-CD19A in combination with R-ICE chemotherapy for second-line DLBCL during 2015.