Elevation Oncology Announces the Presentation of Preclinical Data on the Specific Inhibition of HER3 with Seribantumab to Block NRG1 Fusion Signaling

- Inhibition of HER3 by seribantumab reduces tumor volume by 50-100% in preclinical in vivo models containing an NRG1 fusion -
- Presentation of the data at the 32nd EORTC-NCI-AACR Symposium on Molecular Targets and Cancer Therapeutics -

NEW YORK, Oct. 26, 2020 /PRNewswire/ -- Elevation Oncology , a clinical stage biopharmaceutical company focused on the development of precision medicines for patients with genomically defined cancers, announced today the presentation of preclinical data on the specific inhibition of NRG1 fusion signaling by seribantumab, a HER3 monoclonal antibody, at the 32nd EORTC-NCI-AACR Symposium on Molecular Targets and Cancer Therapeutics (Odintsov et al., 2020). The data support the scientific rationale for the Phase 2 CRESTONE study for patients with solid tumors of any origin that have an NRG1 gene fusion. The CRESTONE study is currently enrolling at sites across the US. Details on the CRESTONE study have recently been presented at both the AACR Virtual Special Conference: Pancreatic Cancer (Bendell et al., 2020) and the North American Conference on Lung Cancer (Spigel et al., 2020).

"The preclinical research on HER3 inhibition in disease models of cancers with *NRG1* gene fusions is encouraging," said Igor Odintsov, MD, Research Fellow, Memorial Sloan Kettering Cancer Center (MSK) and lead author of the abstract, who performed this study with Romel Somwar, PhD, in The Marc Ladanyi Lab at MSK. "The data demonstrate that treatment with seribantumab results in decreased phosphorylation of not only HER3 but also its dimerization partners HER2, HER4, and EGFR, and downstream PI3K and MAPK signaling pathways, suggesting efficient inhibition across HER3 and the entire ERBB signaling pathway. Administration of seribantumab resulted in significant tumor shrinkage of tumors that contain an NRG1 gene fusion in *in vivo* models of lung and ovarian cancer with an approximately 50% and 90-100% tumor reduction, respectively. These results support the potential of HER3 inhibition as a therapeutic strategy in patients that have tumors harboring an NRG1 fusion."

Seribantumab's primary mechanism of action in the NRG1 fusion model is through inhibition of ligand-dependent activation of HER3 (also known as ERBB3). Seribantumab also interferes with the dimerization of HER3 with other ERBB family members and blocks the phosphorylation of all ERBB family members and activation of the PI3K and MAPK downstream signaling pathways.

Seribantumab blocked phosphorylation of HER3, as well as EGFR, HER2, and HER4. Additionally, seribantumab inhibited the activation of downstream effectors including AKT, p70S6 kinase, pERK1/2 and induced pro-apoptotic proteins and activated caspase 3/7 in lung and breast cancer cell lines harboring NRG1 fusions. Additionally, in patient derived xenograft models of ovarian and lung cancer that express an NRG1 gene fusion, seribantumab reduced tumor volume following treatment at clinically relevant doses. This is in contrast to the pan-ERBB inhibitor afatinib, which had a limited effect on the inhibition of tumor growth in the same *in vivo* models when used at the clinically equivalent dose.

"Precise therapy development is needed to ensure that patients and their physicians have treatment options that make their genomic test results actionable," said Lori Kunkel, MD, Chair of the Elevation Oncology Scientific Advisory Board. "These data outline the scientific rationale for targeted inhibition of HER3 when an NRG1 gene fusion is detected. The specific inhibition of HER3 with the monoclonal antibody seribantumab results in significant tumor reduction and sustained disease control in models of cancers driven by an NRG1 gene fusion. These preclinical results are now being clinically evaluated in the Phase 2 CRESTONE study for patients with solid tumors harboring an NRG1 gene fusion."

CRESTONE is a Phase 2 tumor-agnostic trial of seribantumab in patients with any solid tumor that harbors an NRG1 fusion. CRESTONE is currently open and enrolling patients across the US. The primary objective of the study is to describe the Objective Response Rate (ORR) of seribantumab and key secondary endpoints are Duration of Response (DoR) and safety.

"Seribantumab demonstrates significant activity in preclinical models through the destabilization of HER3 and the entire ERBB signaling pathway," said Shawn Leland, PharmD, RPh, Founder and Chief Business Officer of

Elevation Oncology. "In tumors with an NRG1 fusion, HER3 signaling activated by NRG1 fusion proteins is most often the unique oncogenic driver. It is critical for patients to have the appropriate genomic test to detect the presence of an NRG1 fusion and we have partnered with multiple diagnostic companies, major academic centers and community practices to expand access to the CRESTONE study. We believe that this collaborative approach offers the best opportunity to identify patients who may benefit from treatment with seribantumab and allows us to meet them where they are, especially during the time of COVID-19 where immunocompromised patients with cancer are reluctant to travel."

Diagnostic partnerships will enhance traditional patient enrollment in the CRESTONE study through real-time, nationwide identification of NRG1 fusion positive patients within the Ashion Analytics, Strata Oncology, Tempus, Caris Life Sciences, and US Oncology Research partner networks. Through the various partnership models, patients may also be enrolled in CRESTONE either through active referral to current strategic sites or "just-in-time" site initiation within the partner networks.

Patients and physicians can learn more about the CRESTONE study at www.nrg1fusion.com or on www.ClinicalTrials.gov under the NCT number NCT04383210.

About Elevation Oncology
Elevation Oncology is founded on the belief that every patient with cancer deserves to know what is driving the growth of their disease and have access to therapeutics that can stop it. We make genomic tests actionable by selectively developing drugs to inhibit the specific alterations that have been identified as drivers of disease. Together with our peers we work towards a future in which each unique test result can be matched with a purpose-built precision medicine to enable an individualized treatment plan for each patient. Our lead candidate, seribantumab, inhibits tumor growth driven by NRG1 fusions and is currently being clinically tested in the Phase 2 CRESTONE study for patients with tumors of any origin that have an NRG1 fusion. Details on CRESTONE are available at www.NRG1fusion.com. For more information visit www.ElevationOncology.com.

About Seribantumab and NRG1 Gene Fusions
Seribantumab is a fully human IgG2 monoclonal antibody that binds to human epidermal growth factor receptor 3 (HER3). HER3 is traditionally activated through binding of its primary ligand, neuregulin-1 (NRG1). The NRG1 gene fusion is a rare genomic alteration that combines NRG1 with another partner protein to create chimeric NRG1 "fusion proteins". The NRG1 fusion protein is often also able to activate the HER3 pathway, leading to unregulated cell growth and proliferation. Importantly, NRG1 gene fusions are mutually exclusive with other known driver mutations and are considered a unique oncogenic driver event essential for tumor cell survival.

NRG1 fusions have been identified in a variety of solid tumors, including lung, pancreatic, gallbladder, breast, ovarian, colorectal, neuroendocrine, and sarcomas. In preclinical experiments, seribantumab prevents the activation of HER3 signaling in cells that harbor an NRG1 gene fusion. In addition to extensive nonclinical characterization and testing, seribantumab has been administered to 847 patients across 12 phase 1 and 2 studies, both as a monotherapy and in combination with various anticancer therapies. Seribantumab is currently being clinically tested in the Phase 2 CRESTONE study for patients with solid tumors of any origin that have an NRG1 fusion.

About the CRESTONE Study
Clinical Study of Response to Seribantumab in Tumors with Neuregulin-1 (NRG1) Fusions. CRESTONE is a Phase 2 tumor-agnostic "basket trial" of seribantumab in patients with any solid tumor that harbor an NRG1 fusion. The primary objective of the study is to describe the anti-tumor activity and safety of seribantumab specifically in patients with an NRG1 gene fusion. CRESTONE offers a clinical trial opportunity for patients with advanced solid tumors who have not responded or are no longer responding to treatment. Patients are encouraged to talk to their doctor about genomic testing of their tumor. CRESTONE is open and enrolling today in the US. For more information visit www.NRG1fusion.com.

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