IASLC 2020 North America Conference on Lung Cancer
OCTOBER 16-17, 2020 | WORLDWIDE VIRTUAL EVENT
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CRESTONE – Clinical Study of REsponse to Seribantumab in TumOrs with NEuregulin-1 (NRG1) Fusions – A Phase 2 Study of the anti-HER3 mAb for Advanced or Metastatic Solid Tumors (NCT04383210)

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Background: NRG1 Fusions

- NRG1 (Neuregulin-1) gene fusions are rare oncogenic drivers found in 0.2% of solid tumors, including lung, pancreatic, gallbladder, breast, ovarian, colorectal, neuroendocrine, and sarcomas.[1,2]
- NRG1 is the predominant ligand of HER3 and to a lesser extent HER4.
- NRG1 fusion proteins retaining an active EGF-like domain drive tumorigenesis and proliferation through aberrant HER3 activation (**Fig 1**).

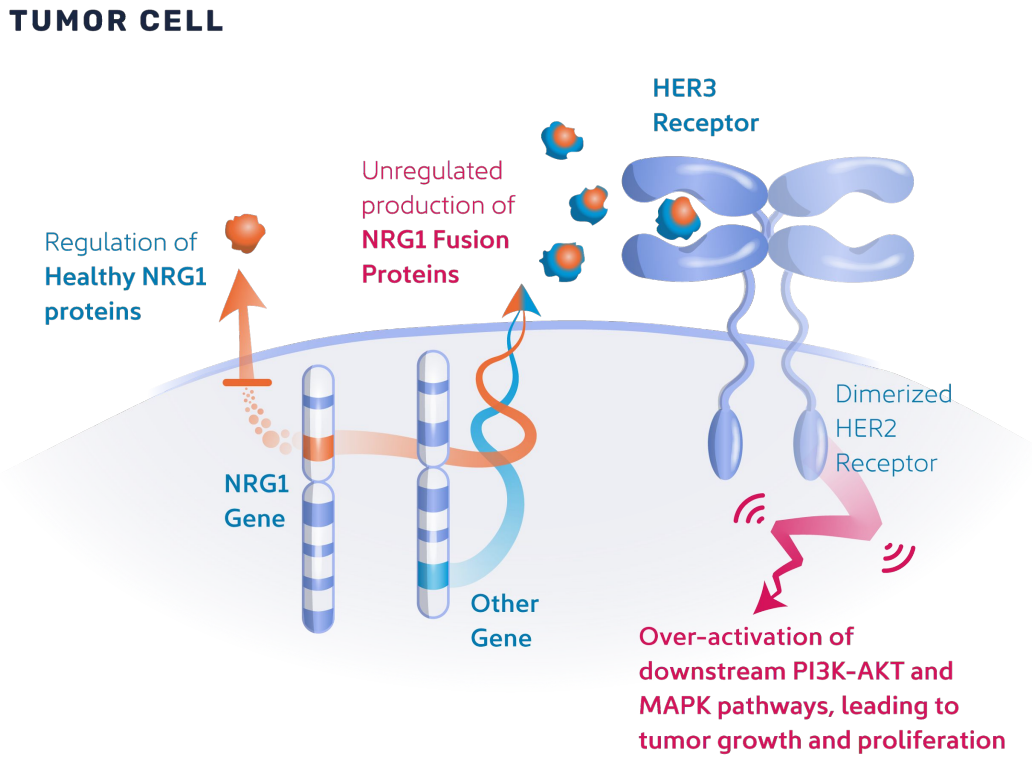


Figure 1. NRG1 fusion activation of HER3 and downstream pathways

Background: Unmet Need for NRG1 Fusions

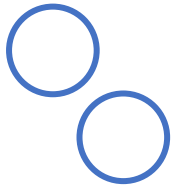
New targeted therapies are needed for the treatment of solid tumors with an NRG1 fusion:

Standard of Care

Patients with NRG1 fusions **do not normally respond well to treatment** with standard chemotherapy, chemoimmunotherapy or novel checkpoint inhibitors such as anti-PD-1/anti-PD-L1 therapies.[3]

OS & DFS

Presence of an NRG1 fusion has been correlated with **worse overall and disease-free survival** when treated with current therapies.[4]



Exclusive with known drivers

Importantly, NRG1 fusions are often **mutually exclusive with other known driver alterations**.[2,5,6]

Background: NRG1 Fusions in Lung Cancer

- NRG1 fusions estimated in 0.8% of lung cancers overall.[7]
- NRG 1 fusions are enriched in the invasive mucinous adenocarcinoma (IMA) subtype, where incidence may be as high as 27-31%.[6]
- **Durable responses (6 to 27+ mths) can be achieved through treatment with anti-HER3 antibodies or pan-ERBB TKIs (Table 1).**

Table 1. Clinical case reports of responses in NRG1 fusion positive lung tumors

Tumor Type	NRG1 Fusion	Response (DoR, mths)	Ref
GSK2849330 (anti-HER3)			
IMA (Lung)	CD74 – NRG1	**PR (19)**	[6]
MCLA-128 (anti-HER2/3 bispecific)			
Lung, unspecified	CD74 – NRG1	**PR (4+, ongoing)**	[8]
Afatinib (Pan-HER TKI)			
Lung adenocarcinoma	SDC4 – NRG1	**PR (12)**	[9]
Lung adenocarcinoma	SLC3A2 – NRG1	**PR (12)**	[10]
Lung adenocarcinoma	CD74 – NRG1	**PR (10)**	
IMA (Lung)	CD74 – NRG1	**PR (6)**	[11]
Lung adenocarcinoma	Unspecified	**PR (24)**	[12]
Lung adenocarcinoma	CD74 – NRG1	**PR (27+, ongoing)**	
IMA (Lung)	CD74 – NRG1	**PR (>18)**	
IMA (Lung)	SDC4 – NRG1	**PR (5, then 6)**	

Background: Seribantumab

- Seribantumab is a fully human IgG2 mAb inhibiting HER3 and downstream pathways through:
  - Inhibition of NRG1-dependent activation of HER3,
  - Inhibition of HER3-HER2 dimerization, and
  - Blocking signaling through the PI3K/AKT and MAPK pathways.
- The safety profile of seribantumab is well characterized through prior monotherapy (N=43) and combination studies in over 800 patients.

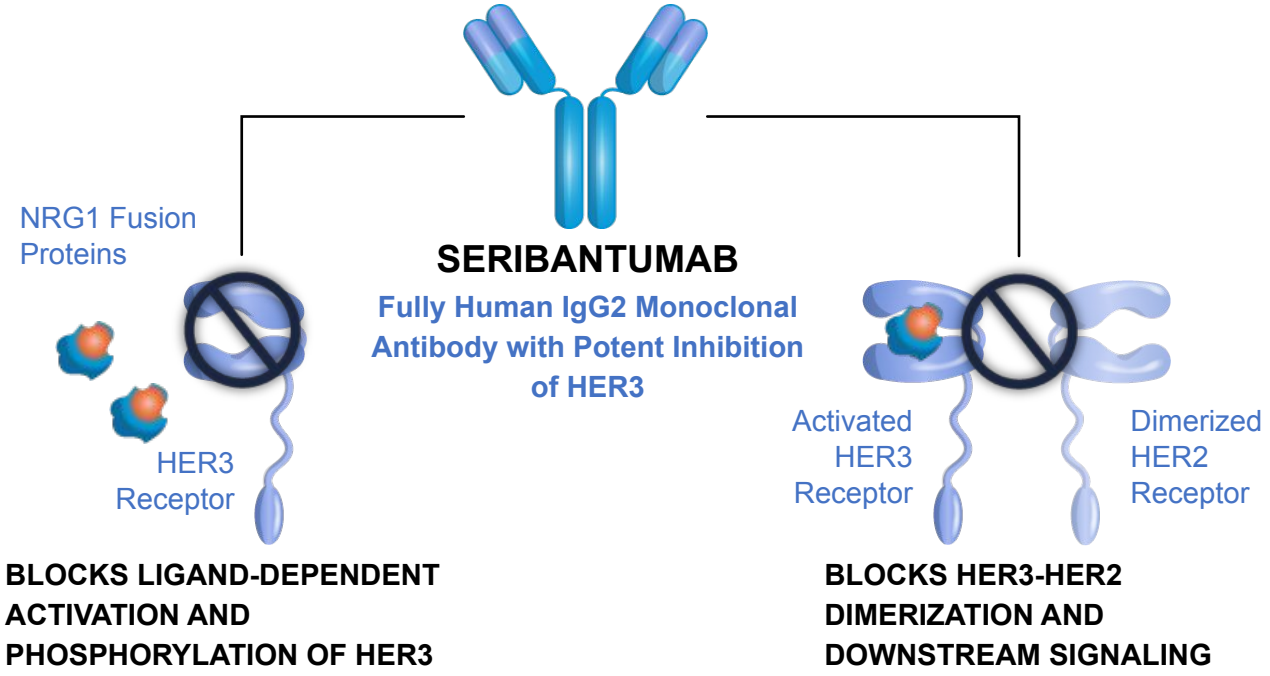
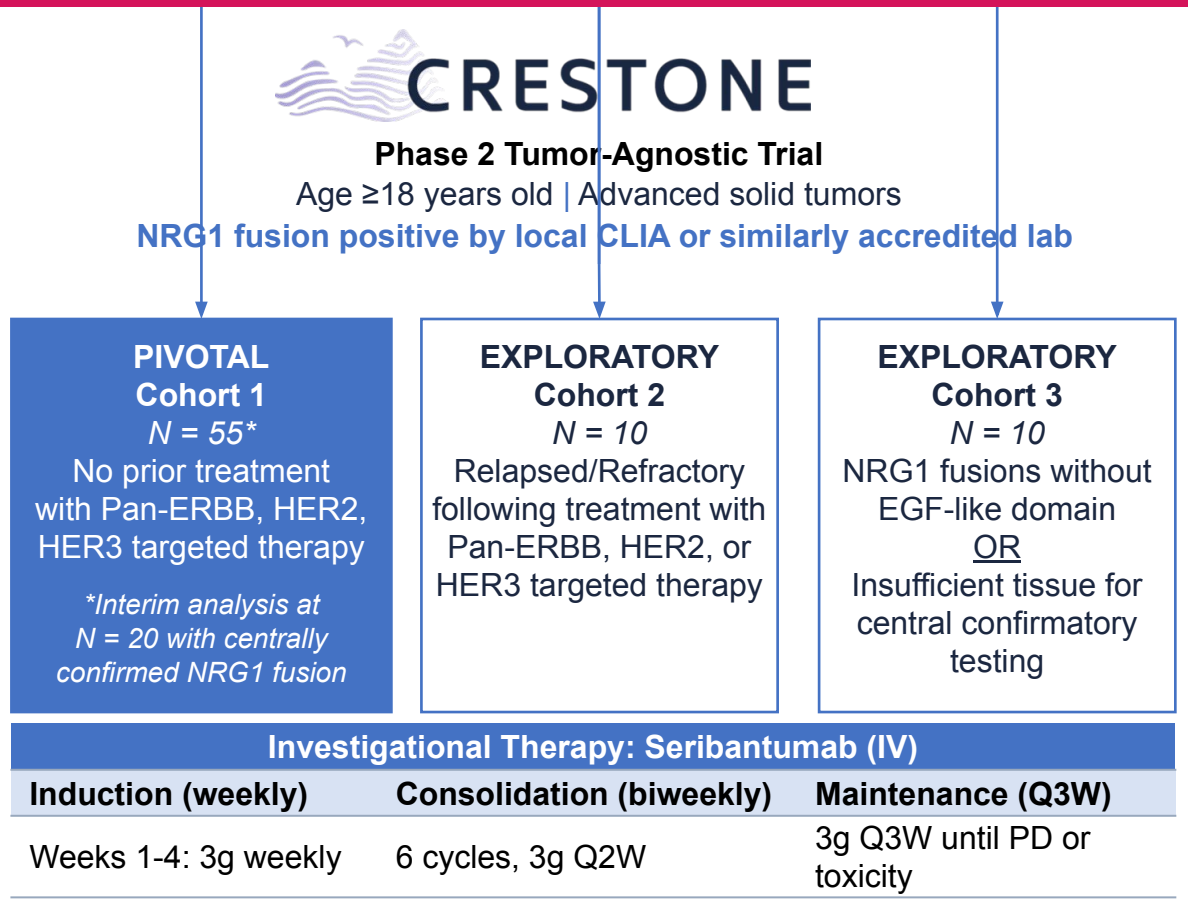


Figure 2. Seribantumab inhibition of HER3 and downstream pathways

Methods: CRESTONE Trial

- Open label, multicenter Phase 2 basket trial of seribantumab in adult patients with NRG1 fusion-positive locally advanced or metastatic solid tumors who have progressed on or are nonresponsive to available therapies.
- Enrolling N=75 patients across three cohorts:
  - **Cohort 1** (N=55): Patients who have not received prior treatment with any ERBB targeted therapy.
  - **Cohort 2** (up to N=10): Patients who have progressed after prior treatment, including prior ERBB targeted therapy.
  - **Cohort 3** (up to N=10): Patients harboring NRG1 fusions without an EGF-like binding domain.
- Novel dosing regimen designed to rapidly achieve steady state levels, optimize exposure, and deliver maximal NRG1 inhibition.



Methods: Key Eligibility Criteria

Key Inclusion Criteria

- ✔ **Locally-advanced or metastatic solid tumor with an NRG1 gene fusion**
- ✔ Fresh or archived FFPE tumor sample
- ✔ Minimum of one prior standard therapy
- ✔ ≥ 18 years of age
- ✔ ECOG performance status: 0, 1, or 2
- ✔ At least one measurable extra-cranial lesion (RECIST)

Key Exclusion Criteria

- Known, actionable oncogenic driver mutation other than NRG1 fusion where available standard therapy is indicated

NRG1 fusion status for enrollment will be determined through a local CLIA or similarly accredited molecular assay.

NRG1 fusion status for patients in Cohort 1 will be centrally confirmed using an RNA-based NGS assay.

Methods: Objectives

Primary endpoint

Objective response rate (ORR) per RECIST v1.1 by independent/central radiologic review.

Secondary endpoints

- Duration of response (DoR)
- Safety
- Progression free survival (PFS)
- Overall survival (OS)
- Clinical Benefit Rate (CR, PD, SD > 24 weeks)

Exploratory endpoints

- Clinical relevance of fusion partners
- Impact of prior therapies, including ERBB targeted therapies
- Resistance mechanisms

Methods: Study Status

CRESTONE is open and enrolling with 25-30 planned sites in the US.

Patient identification and enrollment is enhanced through partnerships enabling targeted patient identification and ”Just in Time” site initiation.

Open sites as of September 7, 2020

Site		Investigator
SARAH CANNON	Sarah Cannon	David Spigel, MD
SITEMAN CANCER CENTER — A NATIONAL CANCER INSTITUTE COMPREHENSIVE CANCER CENTER	Washington University at St. Louis (Siteman Cancer Center)	Saiama N. Waqar, MD
Henry Ford Health System — Henry Ford Cancer Institute	Henry Ford Health System	Shirish Gadgeel, MD
Carbone Cancer Center — University of Wisconsin School of Medicine and Public Health	University of Wisconsin (Carbone Cancer Center)	Mark E. Burkard, MD, PhD

Partnerships as of September 7, 2020

ASHION — A TGen® Clinical Laboratory
CARIS LIFE SCIENCES
STRATA oncology
TEMPUS
US Oncology Research

Conclusions

- NRG1 fusions are an actionable driver alteration across solid tumors.
- Inhibition of HER3 and its dimerization partners represents a rational and novel therapeutic approach for tumors harboring an NRG1 fusion, supported by case studies of clinical responses to therapies targeting ERBB family members.[4,5,7,8]
- CRESTONE is a Phase 2 tumor agnostic study of seribantumab, an anti-HER3 antibody, in patients with solid tumors that harbor an NRG1 fusion.

Learn more about CRESTONE (NCT#04383210) at www.nrg1fusion.com

Contact: clinical@elevationoncology.com or medicalaffairs@elevationoncology.com

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Acknowledgements and Disclosures

Acknowledgements

- The authors would like to thank all patients and supporting staff participating in this study. This study is sponsored by Elevation Oncology, Inc.

Disclosures

- SML and DP are employees of Elevation Oncology.
- LK and SIO serve on the scientific advisory board of Elevation Oncology.