CRESTONE: Clinical Study of REsponse to Seribantumab in TumOrs with NEuregulin-1 (NRG1) Fusions – A Phase II Study of the Anti-HER3 mAb for Advanced or Metastatic Solid Tumors (NCT04383210)

TPS449

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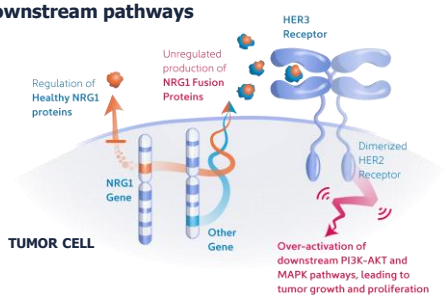
BACKGROUND

NRG1 Fusions

- Neuregulin-1 (NRG1) gene fusions are rare oncogenic drivers found in 0.2% of solid tumors, including pancreatic, gallbladder, colorectal, lung, breast, ovarian, neuroendocrine, and sarcomas.[1,2]
- Patients with tumors bearing NRG1 fusions have limited responses to standard current therapies, as well as poorer disease-free and overall survival than patients without NRG1 fusions.[3,4]
- NRG1 fusion proteins predominantly retain an active EGF-like domain, which drives tumorigenesis and proliferation through aberrant HER3 activation (**Figure 1**). Importantly, NRG1 fusions and other known driver alterations are often mutually exclusive.[2,5,6]

Figure 1. NRG1 fusion activation of HER3 and downstream pathways



NRG1 Fusions in Gastrointestinal Cancers

- NRG1 fusions are enriched in pancreatic ductal adenocarcinoma (PDAC), where the incidence may be as high as 6%.[7]
- NRG1 fusions and KRAS activating mutations in PDAC appear to be mutually exclusive.[7,8]
- Published clinical case reports of gastrointestinal cancers harboring NRG1 fusions suggest that significant responses can be achieved through inhibition of ERBB family members (**Table 1**).

Seribantumab

- Seribantumab is a fully human immunoglobulin G2 (IgG2) monoclonal antibody (mAb) against HER3.
- Seribantumab inhibits NRG1-dependent activation of HER3, HER3-HER2 dimerization, phosphorylation, and signaling with EGFR, HER2 and HER4, and downstream signaling through the phosphoinositide 3-kinases (PI3K/AKT) and mitogen-activated protein kinase (MAPK) pathways in preclinical models *in vitro* and *in vivo*.[5,13] (**Figure 2**).
- Seribantumab inhibited growth, induced pro-apoptotic proteins, and activated caspase 3/7 in NRG1 fusion-positive lung and breast cancer cell lines.[13]

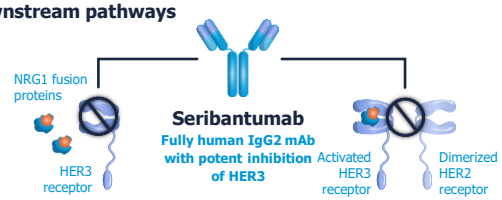
Table 1. Clinical case reports of responses in NRG1 fusion-positive gastrointestinal cancers

Tumor type	NRG1 fusion	Response (DoR, mths)	Ref
Afatinib (pan-HER TKI)			
KRAS-wt Stage IV with liver metastases, PDAC	APP – NRG1	PR (7+, ongoing)	[9]
KRAS-wt Stage IV with liver metastases, PDAC	ATP1B1 – NRG1	PR (5.5)	
KRAS-wt, Stage IV, PDAC	ATP1B1 – NRG1	PR (<5)	[8]
Cholangiocarcinoma	ATP1B1 (E2) – NRG1 (E2)	PR (8)	[10]
KRAS-mutant, stage IVB with liver + lung metastases, CRC	POMK – NRG1	SD (9+, ongoing)	[9]
KRAS-mutant, stage IVB with liver + lung metastases, CRC	POMK – NRG1	SD (16)	[11]
Erlotinib (EGFR TKI) + pertuzumab (mAb preventing dimerization of HER2)			
KRAS-wt, Stage IV, PDAC	SARAF – NRG1	PR (<5)	[8]
MCLA-128 (HER2/HER3 bispecific antibody)			
KRAS-wt Stage IIB, PDAC	ATP1B1 – NRG1	PR (7+, ongoing)	[12]
KRAS-wt Stage IV with liver metastases, PDAC	ATP1B1 – NRG1	SD (7+, ongoing)	

*PR by RECIST v1.1. APP, amyloid precursor protein; ATP1B1, ATPase Na+/K+ transporting subunit beta 1; CRC, colorectal cancer; DoR, duration of response; EGFR, epidermal growth factor receptor; HER, human epidermal growth factor receptor; mAb, monoclonal antibody; mths, months; NRG1, Neuregulin-1; PDAC, pancreatic ductal adenocarcinoma; PR, partial response; Ref, reference; SDC4, Syndecan-4; TKI, tyrosine kinase inhibitor; wt, wildtype.

- Treatment with seribantumab resulted in 60%–100% reduction in tumor volume in NRG1 fusion-positive patient-derived xenograft models of lung and ovarian cancer.[13]
- The clinical safety profile of seribantumab has been well characterized through prior monotherapy and combination studies in over 800 patients.

Figure 2. Seribantumab inhibition of HER3 and downstream pathways



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METHODS

Study Design

CRESTONE is an open-label, multicenter, Phase II 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 (**Figure 3**).

This study will evaluate seribantumab 1-h IV infusion at various doses and schedules to optimize HER3 target inhibition, and enroll at least 75 previously treated patients across 3 cohorts:

Figure 3. Registration-directed Phase II tumor-agnostic trial

Age ≥18 years | Advanced solid tumors

NRG1 fusion-positive by local CLIA or similarly accredited lab

PIVOTAL
Cohort 1
n=55*
No prior treatment with pan-ERBB, HER2, or HER3 targeted therapy
**Interim analysis at n=20 with centrally confirmed NRG1 fusion*

EXPLORATORY
Cohort 2
n=10
Relapsed/refractory following standard treatment, which included treatment with pan-ERBB, HER2, and/or HER3 targeted therapy

EXPLORATORY
Cohort 3
n=10
NRG1 fusions without EGF-like domain OR insufficient tissue for central confirmatory testing

Key Eligibility Criteria

- Locally advanced or metastatic solid tumor with an NRG1 gene fusion.
- Fresh or archived formalin-fixed, paraffin-embedded tumor sample.
- Minimum of 1 prior standard therapy.
- ≥18 years of age.
- Eastern Cooperative Oncology Group (ECOG). performance status: 0, 1, or 2.
- At least 1 measurable extra-cranial lesion per Response Evaluation Criteria In Solid Tumors version 1.1 (RECIST v1.1).

NRG1 fusion status for enrollment will be determined through a local Clinical Laboratory Improvement Amendments or similarly accredited molecular assay. NRG1 fusion status for patients in Cohort 1 will be centrally confirmed using an RNA-based next-generation sequencing assay.

Study Status

- Open and enrolling with 25–30 planned sites in the USA.
- Patient identification and enrollment enhanced through partnerships with Ashion Analytics, Caris Life Sciences, Strata Oncology, Tempus, and US Oncology Research.

Objectives

- **CRESTONE is designed with registration-directed intent for a tumor-agnostic indication**
  - NRG1 fusion status will be centrally confirmed using RNA-based sequencing.
- **Primary endpoint:** Objective response rate per RECIST v1.1 by independent/central radiologic review.
- **Secondary endpoints:** Duration of response, safety, progression-free survival, overall survival, clinical benefit rate (complete response, disease progression + stable disease >24 weeks).
- Multi-cohort design and sample collection enables exploratory investigation of:
  - Clinical relevance of fusion partners.
  - Impact of prior therapies, including ERBB, HER2, and HER3 targeted therapies.
  - Resistance mechanisms.

DISCLOSURES

Study sponsored by Elevation Oncology Inc. Aurora, CO. JCB received funds from Merck, Genentech/Roche, Celgene, Daiichi Sankyo, Gilead Sciences, Bristol-Myers Squibb, Lilly, MedImmune, Taiho Pharmaceutical, Novartis, OncoMed, Boehringer Ingelheim, ARMO BioSciences, Ipsen, and FORMA Therapeutics. SML and DP are employees of Elevation Oncology; SML received funds, holds stock, and has patents with Verastem and Elevation Oncology. K-HL, MEB, SJK, MAS, SMG, KLR, LAK, ED, GAO, S-HIO, TP, JH, ESK declare receiving funds for services such as consultant, Speaker' Bureau, or research funding, hold stocks, or have patients with other pharmaceutical companies. See QR code for full disclosures.

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- K-HL received research funding from Aclaris Therapeutics
- MEB served as a consultant for Pointcare Genomics, Strata Oncology, and Novartis, and has patents for an implantable/localize drug delivery device and a method to detect recombination events
- SJK served as a consultant/Speakers' Bureau for Lilly, Boston Biomedical, Astellas Pharma, Foundation Medicine, Bristol-Myers Squibb, Pieris Pharmaceuticals, and Merck, received funds from Natera, holds stock with Turning Points Therapeutics, and other with NCCN
- MAS served as a consultant/Speakers' Bureau for Genentech, AstraZeneca, MedImmune, Lilly, Janssen, Bristol-Myers Squibb, Boehringer Ingelheim, Bayer, Merk and Novartis, and received funds from Genentech, Bristol-Myers Squibb, Celgene, AstraZeneca, Guardant Health, Bayer, Merck, Roche/Genentech, and Lilly
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- SML is an employee of Elevation Oncology, received funds, holds stock, and has patents with Verastem and Elevation Oncology
- DP is an employee at Elevation Oncology, and Global Biotechnology & Cancer Therapeutics
- LAK served as a consultant for Principa Biopharma and Takeda, and holds stocks with Curis, Nurix, ORIC Pharmaceuticals, Atreca, and Harpoon Therapeutics
- ED received honoraria/research funding from Pfizer, Boston Biomedical, Bayer, Incyte, Merk, MedImmune, GlaxoSmithKline, Lilly, and AstraZeneca
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- JH served as a consultant to AstraZeneca, Bristol-Myers Squibb, Spectrum Pharmaceuticals, Guardant Health, Hengrui Pharmaceutical, GlaxoSmithKline, EMD Serono, Lilly, Syntha Pharmaceutical, Takeda, Sanofi/Aventis, and Genentech/Roche, received research funding from AstraZeneca, Spectrum Pharmaceuticals, Bayer, and GlaxoSmithKline, hold stocks with Cardinal Spine and Bio-Tree, and has licensing agreement regarding treatment of EGFR and HER2 exon 20 mutations
- ESK served as a consultant and received honoraria from AstraZeneca, Boehringer Ingelheim, Pfizer, Merk, Takeda, Genentech/Roche, and received research funding from Boehringer Ingelheim, Merk, Ignyta, and Roche/Genentech