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)

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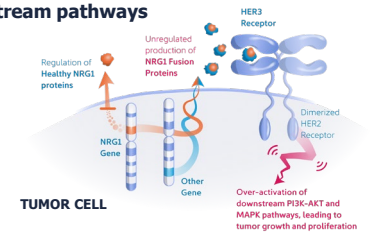
BACKGROUND

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 harboring NRG1 fusions have limited responses to standard current therapies, as well as poorer overall and disease-free 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/ERBB3 activation (**Figure 1**). NRG1 fusions are mutually exclusive with most other known oncogenic drivers.[2,5,6]

Figure 1. NRG1 fusion activation of HER3 and downstream pathways



- NRG1 fusions have been found in **0.4%** of ovarian cancers and **0.2%** of breast cancers.[2]
- Published clinical case reports of cancers harboring NRG1 fusions, including ovarian cancer, suggest that durable responses can be achieved through inhibition of ERBB family members (**Table 1**).

Seribantumab

- Seribantumab is a fully humanized immunoglobulin G2 (IgG2) monoclonal antibody (mAb) targeting HER3 (**Figure 2**).
- Seribantumab blocks ligand-dependent activation of HER3, HER3-HER2 dimerization, HER3 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 vitro* and *in vivo*.[5,7]

Figure 2. Seribantumab inhibition of HER3 and downstream pathways

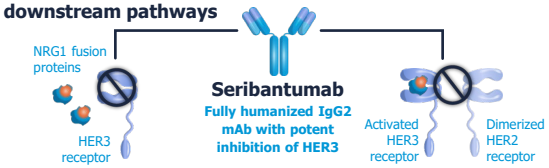


Table 1. Clinical case reports of best responses in patients with cancers harboring NRG1 fusions

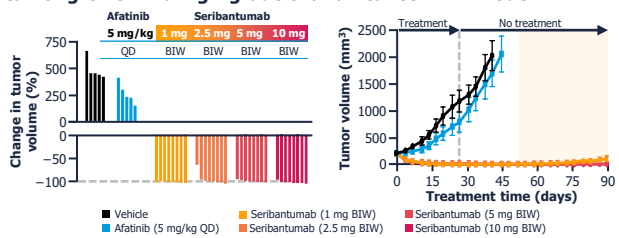
Tumor type	NRG1 fusion	Response (DoR, months)	Source
Afatinib (pan-HER TKI)			
Lung adenocarcinoma	SDC4 (Exon 2) – NRG1 (Exon 4)	PR (12)	[8]
Cholangiocarcinoma	ATP1B1 (Exon 2) – NRG1 (Exon 2)	PR† (8)	
Lung adenocarcinoma	SLC3A2 – NRG1	PR† (12)	[9]
Lung adenocarcinoma	CD74 – NRG1	PR† (10)	
IMA (lung)	CD74 – NRG1	PR† (6)	[10]
PDAC (pancreatic)	ATP1B1 – NRG1	PR† (<5)	[11]
PDAC with liver metastasis	APP (Exons 15/16) – NRG1 (Exons 6/7)	PR† (7+, ongoing)	[12]
PDAC with liver metastasis	ATP1B1 (Exon 3) – NRG1 (Exon 2)	PR† (5.5)	
Lung adenocarcinoma	Unspecified	PR (24)	[13]
Lung adenocarcinoma	CD74 – NRG1	PR (27+, ongoing)	
IMA (lung)	CD74 – NRG1	PR (>18)	
IMA (lung)	SDC4 – NRG1	PR (5, then 6)	
Afatinib + trastuzumab (anti-HER2) + pertuzumab (mAb preventing dimerization of HER2)			
Ovarian‡	CLU – NRG1	SD (>36)	[14]
Erlotinib (EGFR TKI) + pertuzumab			
Pancreatic	SARAF – NRG1	PR (<5)	[11]
GSK2849330 (anti-HER3)			
IMA (lung)	CD74 – NRG1	PR (19)	[6]
MCLA-128 (HER2/HER3 bispecific antibody)			
PDAC	ATP1B1 – NRG1	PR (7+, ongoing)	[15]
NSCLC	CD74 – NRG1	PR (4.5+, ongoing)	

†PR based on clinical details given. ‡First published case report of a patient with ovarian cancer harboring an NRG1 fusion. APP, amyloid precursor protein; ATP1B1, ATPase Na+/K+ transporting subunit beta 1; CD74, cluster of differentiation 74; CLU, clusterin; DoR, duration of response; EGFR, epidermal growth factor receptor; HER, human epidermal growth factor receptor; IMA, invasive mucinous adenocarcinoma; mAb, monoclonal antibody; NRG1, Neuregulin-1; NSCLC, non-small cell lung cancer; PDAC, pancreatic ductal adenocarcinoma; PR, partial response; SARAF, store-operated calcium entry associated regulatory factor; SD, stable disease; SDC4, Syndecan-4; TKI, tyrosine kinase inhibitor.

Prior Experience With Seribantumab

- In breast cancer cell lines harboring NRG1 fusions, seribantumab inhibited growth, induced pro-apoptotic proteins, and activated caspases 3/7.[7]
- Treatment with seribantumab (1–10 mg/mouse bi-weekly) resulted in a substantial reduction in tumor volume and inhibited tumor growth in a patient-derived xenograft (PDX) model harboring a CLU-NRG1 fusion.[7]
  - Tumor size did not regress with afatinib treatment (5 mg/kg once daily; equivalent to 40 mg once daily clinical dose; **Figure 3**).

Figure 3. Seribantumab reduced tumor volume and inhibited tumor growth in a high-grade ovarian cancer PDX model[7]



- The clinical safety profile of seribantumab has been well characterized in over 800 patients through prior monotherapy and combination trials.

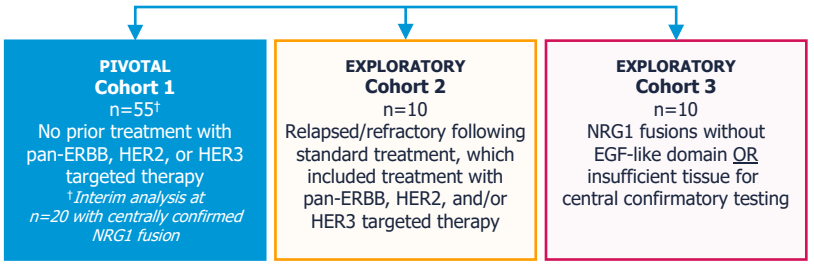
METHODS

Study Design

CRESTONE is an open-label, multicenter, Phase 2 basket trial of seribantumab in adult patients with locally advanced or metastatic solid tumors harboring an NRG1 fusion who have progressed on, or are nonresponsive to, available therapies (**Figure 4**).

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

Figure 4. Registration-directed Phase 2 tumor-agnostic trial



Key Eligibility Criteria

- Locally advanced or metastatic solid tumor harboring 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 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 (CLIA) or similarly accredited molecular assay. NRG1 fusion status in Cohort 1 patients 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 as a tumor-agnostic trial for all patients with solid tumors that harbor NRG1 gene fusions**
  - 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.

REFERENCES

1. Jonna S et al. *J Clin Oncol.* 2020;38(15_suppl):3113.
2. Jonna S et al. *Clin Cancer Res.* 2019;25:4865–4867.
3. Duruisseaux M et al. *J Clin Oncol.* 2019;37(15_suppl):9081.
4. Shin DH et al. *Oncotarget.* 2016;7:69450–69465.
5. Fernandez-Cuesta L et al. *Clin Cancer Res.* 2015;21:1989–1994.
6. Drilon A et al. *Cancer Discov.* 2018;8:686–695.
7. Odintsov I et al. *Eur J Cancer.* 2020;138(Suppl 2):S15–S16.
8. Jones MR et al. *Ann Oncol.* 2017;28:3092–3097.
9. Gay ND et al. *J Thorac Oncol.* 2017;12:e107–e110.
10. Cheema PK et al. *J Thorac Oncol.* 2017;12:e200–e202.
11. Heining C et al. *Cancer Discov.* 2018;8:1087–1095.
12. Weinberg BA et al. ESMO 2019. Abstract P-291.
13. Cadranel J et al. *Oncologist.* 2020;25:[Epub ahead of print].
14. Murumägi A et al. *Cancer Res.* 2019;79(Suppl 13).
15. Schram AM et al. AACR-NCI-EORTC 2019. Abstract PR02.

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