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

Natasha B. Leighl, MD[1], Janessa J. Laskin, MD, FRCPC[2], Randeep Sangha, MD[3], Shawn M. Leland, PharmD, RPh[4], Valerie M. Jansen, MD, PhD[4], Parneet Cheema, MD[5], Brandon S. Sheffield, MD[5], Jose Monzon, PhD, MD, FRCPC[6]

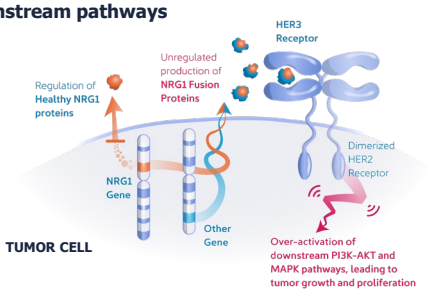
[1]Princess Margaret Cancer Centre, Toronto, ON, Canada [2]BC Cancer, Vancouver, BC, Canada [3]Cross Cancer Institute, Alberta Health Services, Edmonton, AB, Canada [4]Elevation Oncology, LLC, New York, NY, USA, [5]William Osler Health System, Etobicoke, ON, Canada [6]Tom Baker Cancer Centre, Alberta Health Services, University of Calgary, Calgary, AB, Canada

BACKGROUND

NRG1 Fusions

- Neuregulin-1 (NRG1) gene fusions are rare oncogenic drivers found in ~0.2–0.5% 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 worse overall and disease-free survival than patients without NRG1 fusions[3,4]
- NRG1 fusion proteins predominantly retain an active epidermal growth factor (EGF)-like domain, which drives tumorigenesis and proliferation through aberrant human epidermal growth factor receptor (HER)3/ERBB3 activation (**Figure 1**). NRG1 fusions are often mutually exclusive of most other known oncogenic drivers[2,5,6]

Figure 1. NRG1 fusion activation of HER3 and downstream pathways



- Case reports highlight the potential for targeting HER (ERBB) in NRG1 fusions across solid tumor types (**Table 1**)

Seribantumab

- Seribantumab is a fully human 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

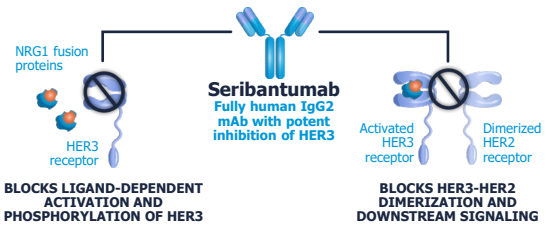


Table 1. Clinical case reports of best responses in patients with cancers harboring NRG1 fusions

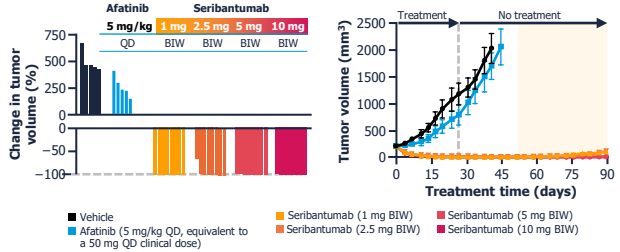
Tumor type	NRG1 fusion	Response (DoR, months)	Source
Afatinib (pan-HER TKI)			
Lung adenocarcinoma	SDC4 (exon 2) – NRG1 (exon 4)	PR (12)	[8]
Cholangiocarcinoma	ATP1B1 (exon 2) – NRG1 (exon 2)	PR† (8)	
Lung adenocarcinoma	SLC3A2 – NRG1	PR† (12)	[9]
Lung adenocarcinoma	CD74 – NRG1	PR† (10)	
IMA (lung)	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

- Treatment of mice bearing patient-derived xenograft (PDX) tumors harboring NRG1 fusions with seribantumab resulted in reductions in tumor volume of up to 100% in ovarian (CLU-NRG1, **Figure 3**), 57% in lung (SLC3A2-NRG1), and 55% in pancreatic cancers (APP-NRG1 rearrangement)[7,16]
- Treatment with seribantumab through an expanded access program resulted in durable disease control for >9 months including partial response in a patient with pancreatic adenocarcinoma with an ATP1B1-NRG1 fusion[17]
- The clinical safety profile of seribantumab has been well characterized in over 800 patients through prior monotherapy and combination trials[18]

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



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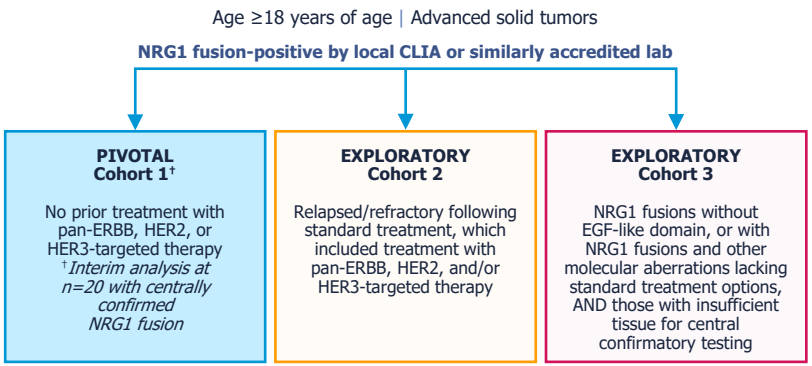
METHODS

Study Design

CRESTONE (NCT04383210) is an open-label, international, multicenter, pivotal Phase 2 trial of seribantumab in adult patients with locally advanced or metastatic solid tumors harboring an NRG1 fusion who have progressed on, or are non-responsive to, available therapies (**Figure 4**). This trial will evaluate 3 g seribantumab 1-h intravenous infusion once weekly, until patients meet 1 or more protocol-specific treatment discontinuation criteria. Patients will be assigned to one of 3 cohorts:

Figure 4. Phase 2 CRESTONE 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 (Cohort 1 only)
- 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 will be determined through molecular assays by a local Clinical Laboratory Improvement Amendments (CLIA) or similarly accredited lab. NRG1 fusion status in Cohort 1 patients will be centrally confirmed by using an RNA-based next-generation sequencing assay

Study Status

- Open and enrolling with ≥30 planned sites in the USA; to open in Canada and Australia in 4Q21
- Patient identification and enrollment enhanced through partnerships with Ashion Analytics, Caris Life Sciences, Exactis Innovation, GTC, NeoGenomics, PathGroup, 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, partial response + 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

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