#COSA21

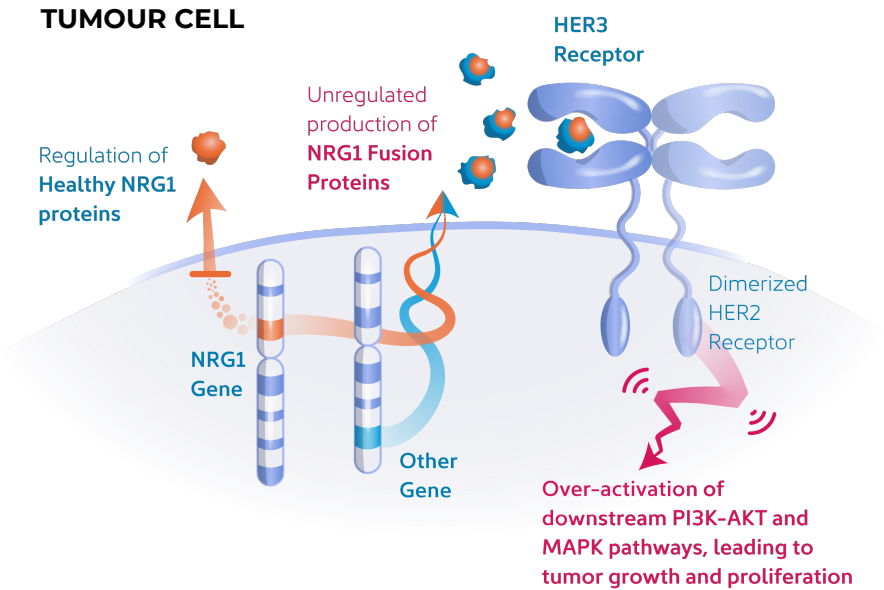
CRESTONE – **C**linical Study of **RE**sponse to Seribantumab in **T**um**O**urs with **NE**uregulin-1 (NRG1) Fusions – A phase 2 study of the anti-HER3 monoclonal antibody for advanced or metastatic solid tumours (MoST CRESTONE in Australia)

Subotheni Thavaneswaran[1–3], Lucille Sebastian[2], Sarah Finlayson[2], Jayesh Desai[4], Ken O'Byrne[5], Rosemary Harrup[6], Mandy L. Ballinger[3], Frank Lin[2,3], John P. Grady[3], Maya Kansara[3], John Simes[2], Shawn M. Leland[7], Valerie M. Jansen[7], David M. Thomas[1,3]

[1]The Kinghorn Cancer Centre, St Vincent's Hospital Sydney, NSW, Australia; [2]NHMRC Clinical Trials Centre, University of Sydney, Sydney, NSW, Australia; [3]Garvan Institute of Medical Research, St Vincent's Clinical School, Faculty of Medicine, University of NSW, NSW, Australia; [4]Department of Medical Oncology, Peter MacCallum Cancer Centre, Melbourne, VIC, Australia; [5]Princess Alexandra Hospital, QLD, Australia; [6]Royal Hobart Hospital, Hobart, Australia; [7]Elevation Oncology, LLC., New York, NY, USA

Clinical NRG1 gene fusions are emerging as rare but potentially actionable oncogenic drivers

- NRG1 gene fusions are rare oncogenic drivers found in ~0.2–0.5% of solid tumours[1,2]
- Patients with tumours harbouring NRG1 fusions have limited responses to standard current therapies, as well as worse overall and disease-free survival than patients without these fusions[3,4]
- NRG1 fusion proteins predominantly retain an active EGF-like domain, which drives tumorigenesis and proliferation through aberrant HER3/ERBB3 activation[1,2,5]
- NRG1 fusions are often mutually exclusive of most other known oncogenic drivers[2,5,6]



NRG1 fusions activate HER3 and downstream pathways

EGF, epidermal growth factor; HER, human epidermal growth factor receptor; NRG1, neuregulin-1

1. Laskin J et al. *Ann Oncol*. 2020;31:1693–1703; 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

Case studies highlight the potential for targeting HER (ERBB) in NRG1 fusions across solid tumour types

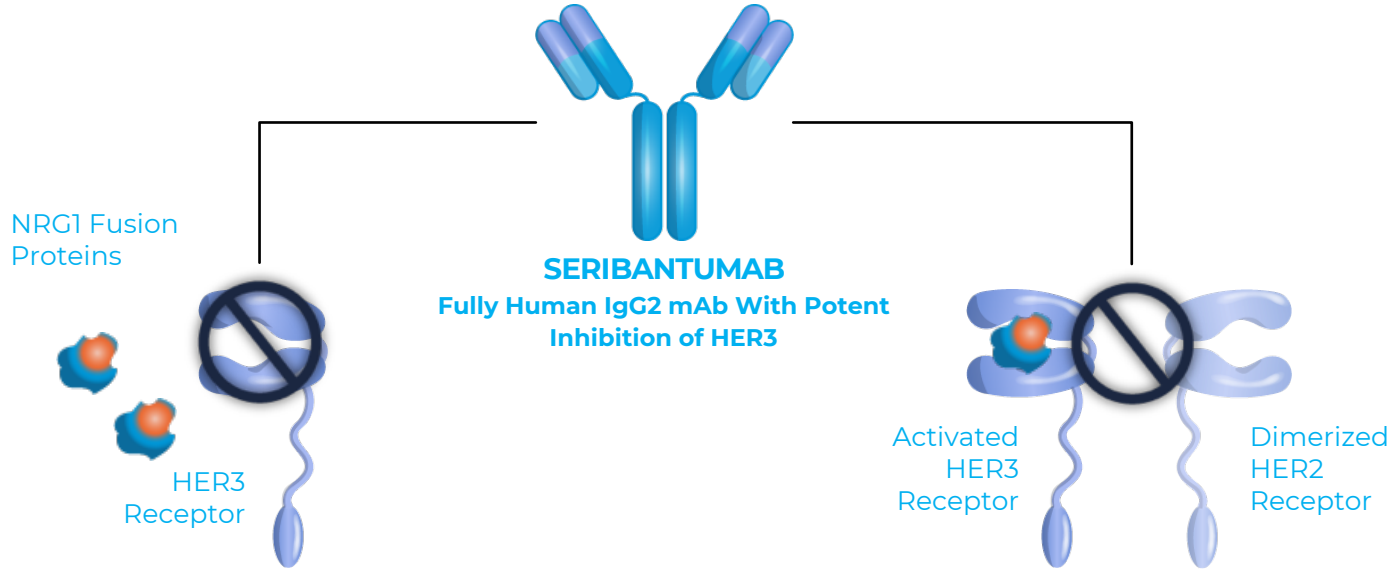
Clinical case reports of best responses in patients with cancers harbouring NRG1 fusions

Tumour type	NRG1 fusion	Response (DoR, months)	Source
Afatinib (pan-HER TKI)			
Lung adenocarcinoma	SDC4 (exon 2) – NRG1 (exon 4)	PR (12)	[1]
Cholangiocarcinoma	ATP1B1 (exon 2) – NRG1 (exon 2)	PR (8)	
Lung adenocarcinoma	SLC3A2 – NRG1	PR (12)	[2]
Lung adenocarcinoma	CD74 – NRG1	PR (10)	
IMA (lung)	CD74 – NRG1	PR (6)	[3]
PDAC (pancreatic)	ATP1B1 – NRG1	PR (<5)	[4]
PDAC with liver metastasis	APP (exons 15/16) – NRG1 (exons 6/7)	PR (7+, ongoing)	[5]
PDAC with liver metastasis	ATP1B1 (exon 3) – NRG1 (exon 2)	PR (5.5)	
Lung adenocarcinoma	Unspecified	PR (24)	[6]
Lung adenocarcinoma	CD74 – NRG1	PR (27+, ongoing)	
IMA (lung)	CD74 – NRG1	PR (>18)	
IMA (lung)	SDC4 – NRG1	PR (5, then 6)	
Erlotinib (EGFR TKI) + pertuzumab			
Pancreatic	SARAF – NRG1	PR (<5)	[4]
GSK2849330 (anti-HER3 antibody)			
IMA (lung)	CD74 – NRG1	PR (19)	[7]
MCLA-128 (HER2/HER3 bispecific antibody)			
PDAC	ATP1B1 – NRG1	PR (7+, ongoing)	[8]
Non-small cell lung cancer	CD74 – NRG1	PR (4.5+, ongoing)	

DoR, duration of response; EGFR, epidermal growth factor receptor; HER, human epidermal growth factor receptor; IMA, invasive mucinous adenocarcinoma; NRG1, neuregulin-1; PDAC, pancreatic ductal adenocarcinoma; PR, partial response; TKI, tyrosine kinase inhibitor. 1. Jones MR et al. *Ann Oncol*. 2017;28:3092–3097; 2. Gay ND et al. *J Thorac Oncol*. 2017;12:e107–e110; 3. Cheema PK et al. *J Thorac Oncol*. 2017;12:e200–e202; 4. Heining C et al. *Cancer Discov*. 2018;8:1087–1095; 5. Weinberg BA et al. ESMO 2019. Abstract P-291; 6. Cadranel J et al. *Oncologist* 2021;26:7–16; 7. Drilon A et al. *Cancer Discov*. 2018;8:686–695; 8. Schram AM et al. AACR-NCI-EORTC 2019. Abstract PR02

Seribantumab (anti-HER3 IgG2 mAb)

Seribantumab is a fully human IgG2 mAb that targets HER3 in multiple ways



BLOCKS LIGAND-DEPENDENT ACTIVATION AND PHOSPHORYLATION OF HER3

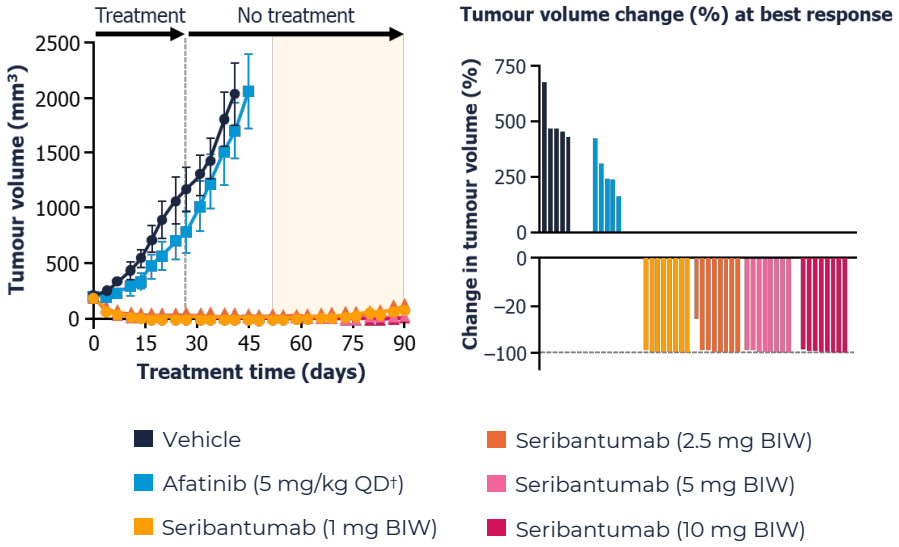
BLOCKS HER3-HER2 DIMERISATION AND DOWNSTREAM SIGNALING

HER, human epidermal growth factor receptor; IgG2, immunoglobulin G2; mAb, monoclonal antibody; NRG1, neuregulin-1

Prior experience with seribantumab

- Treatment with seribantumab resulted in notable reductions in tumour volume in various mouse PDX models harbouring NRG1 fusions:
  - Ovarian cancer (CLU-NRG1), 100%[1]
  - Lung cancer (SLC3A2-NRG1), 57%[1]
  - Pancreatic cancer (APP-NRG1 rearrangement), 55%[2]
- In Australia, treatment with seribantumab through an expanded access program resulted in:
  - Partial response in a patient with pancreatic adenocarcinoma with an ATP1B1-NRG1 fusion[3]
  - Durable disease control for >9 months[3]
- The clinical safety profile of seribantumab has been well characterised in >800 patients through prior monotherapy and combination trials[4]

Seribantumab reduced tumour volume and inhibited tumour growth in a high-grade ovarian cancer (CLU-NRG1) PDX model[1]



†Equivalent to a 50 mg QD clinical dose

APP, amyloid precursor protein; BIW, twice weekly; CLU, clusterin; NRG1, neuregulin-1; PDX, patient-derived xenograft; QD, once daily; SLC3A2, solute carrier family 3 member 2

1. Odintsov I et al. *Eur J Cancer*. 2020;138(Suppl 2):S15–S16; 2. Odinstov I et al. AACR 2021. Abstract 935; 3. Chen WY, et al. AGITG 2021. Abstract. 4. Denlinger CS et al. *Invest New Drugs* 2021. Epub 2021/07/11

CRESTONE: An open-label, international, multicentre, pivotal, phase 2 trial of seribantumab

Key eligibility criteria

- Locally advanced or metastatic solid tumours harbouring an NRG1 gene fusion
- Fresh or archived formalin-fixed, paraffin-embedded tumour sample (Cohort 1 only)
- Minimum of 1 prior standard therapy
- ≥18 years of age
- ECOG PS: 0, 1, or 2
- At least 1 measurable extra-cranial lesion per RECIST v1.1

Phase 2 CRESTONE tumour-agnostic trial

Age ≥18 years of age | Advanced solid tumours

NRG1 fusion-positive by local CLIA†

PIVOTAL Cohort 1 ‡

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

EXPLORATORY Cohort 2

Relapsed/refractory following standard treatment, which included treatment with pan-ERBB, HER2, and/or HER3-targeted therapy

EXPLORATORY Cohort 3

NRG1 fusions without EGF-like domain, or with NRG1 fusions and other molecular aberrations lacking standard treatment options, AND those with insufficient tissue for central confirmatory testing

NRG1 fusion status for enrolment will be determined through molecular assays by a CLIA† certified lab

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

†CLIA or similarly accredited lab; ‡Interim analysis following enrolment of 20 centrally confirmed Cohort 1 patients receiving the optimised regimen of 3g once weekly

CLIA, Clinical Laboratory Improvement Amendments; ECOG PS, Eastern Cooperative Oncology Group Performance Status; EGF, epidermal growth factor; HER, human epidermal growth factor receptor; NGS, next-generation sequencing; NRG1, neuregulin-1; RECIST, Response Evaluation Criteria In Solid Tumours

CRESTONE: Clinical study of response to seribantumab in tumours harbouring NRG1 fusions

Objective

To evaluate a 3-g seribantumab 1-h IV infusion once weekly, until patients meet 1 or more protocol-specific treatment discontinuation criteria

Primary endpoint

ORR per RECIST v1.1 by independent/central radiologic review

Secondary endpoints

- DoR
- Safety
- PFS
- OS
- Clinical Benefit Rate (CR, PR, SD >24 weeks)
- TTP2/TTP1†
- PFS at 6 months†
- OS at 12 months†

Exploratory endpoints

- Clinical relevance of fusion partners
- Impact of prior therapies, including ERBB, HER2, and HER3-targeted therapies
- Resistance mechanisms

Study status

- CRESTONE is accruing patients globally in the USA (active), Australia through the Molecular Screening and Therapeutics (MoST) program as MoST CRESTONE (active in Q4 2021), and Canada (active in Q4 2021)
- Patient identification and enrolment enhanced through partnerships with Ashion Analytics, Caris Life Sciences, Omico, Strata Oncology, Tempus, and US Oncology Research

†Additional secondary endpoint for MoST CRESTONE
CR, complete response; DoR, duration of response; HER, human epidermal growth factor receptor; IV, intravenous; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; SD, stable disease; TTP1, time to progression in the period prior to MoST CRESTONE; TTP2, time to progression on MoST CRESTONE

#COSA21

Summary

- NRG1 fusions are potentially actionable driver alterations across solid tumours and appear to be mutually exclusive of most other known mutations
- Inhibition of HER3 and its dimerisation partners represents a rational and novel therapeutic approach for tumours harbouring an NRG1 fusion, supported by case studies of clinical responses to therapies targeting ERBB family members[1–8]
- CRESTONE is a Phase 2 tumour-agnostic study of seribantumab, a fully human IgG2 mAb targeting HER3, in patients with solid tumours harbouring an NRG1 fusion
- MoST CRESTONE will open in Australia in Q4 2021

Learn more about CRESTONE† (NCT04383210) at www.nrg1fusion.com

†The CRESTONE study is sponsored globally by Elevation Oncology. In Australia, the study (known as MoST CRESTONE) is sponsored by the University of Sydney.

HER, human epidermal growth factor receptor; IgG2, immunoglobulin G2; mAb, monoclonal antibody; NRG1, neuregulin-1

1. Jones MR et al. *Ann Oncol*. 2017;28:3092–3097; 2. Gay ND et al. *J Thorac Oncol*. 2017;12:e107–e110; 3. Cheema PK et al. *J Thorac Oncol*. 2017;12:e200–e202; 4. Heining C et al. *Cancer Discov*. 2018;8:1087–1095; 5. Weinberg BA et al. ESMO 2019. Abstract P-291; 6. Cadranel J et al. *Oncologist* 2021;26:7–16; 7. Drilon A et al. *Cancer Discov*. 2018;8:686–695; 8. Schram AM et al. AACR-NCI-EORTC 2019. Abstract PR02