NRG1 FUSIONS

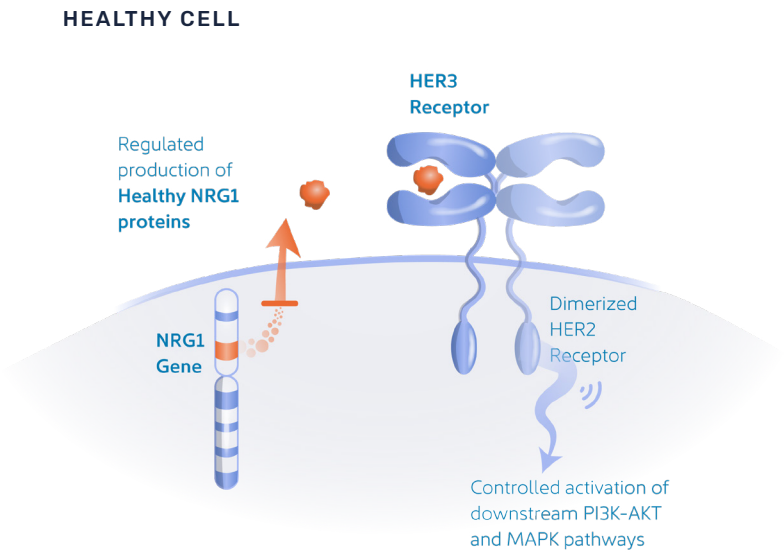
The science behind the CRESTONE study

Neuregulin-1 (NRG1)

NRG1 is an abbreviation for **neuregulin-1**, sometimes also called *heregulin.*

Healthy cells throughout the body use the genomic information in the NRG1 gene to create NRG1 proteins, which perform a wide variety of functions and are essential for normal development of the nervous system and heart.

Healthy NRG1 proteins bind to the HER3 receptor on the surface of a cell. This signals the cell to perform certain actions important to its survival and proliferation. Cells normally regulate the creation of normal NRG1 proteins to avoid unchecked growth.

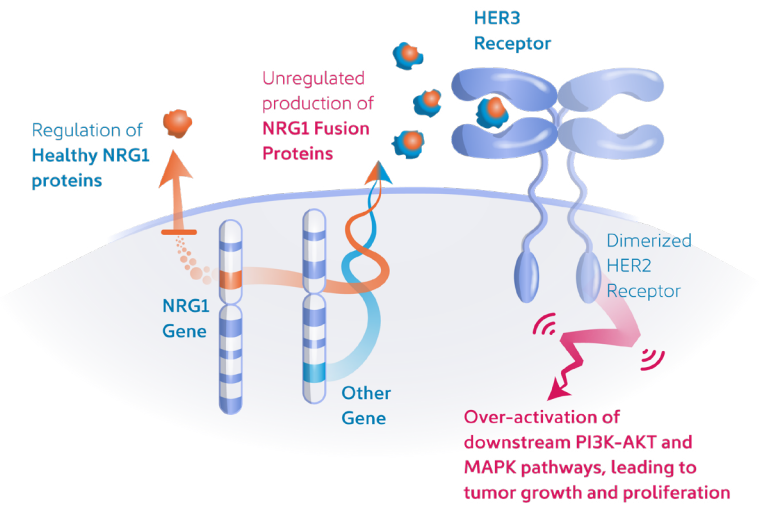


NRG1 Fusions

NRG1 fusion proteins contain components of both the NRG1 protein and another protein. They are made when a cell has a genomic alteration called an **NRG1 gene fusion** that causes it to combine the information in the NRG1 gene with information in another gene.

NRG1 fusion proteins that retain their active component, known as the EGF-like domain, can continue to bind to HER3 like a normal NRG1 protein. However, this means they can activate HER3 in an unregulated way.

Unregulated activation of HER3 by NRG1 fusion proteins can cause a normal cell to transform into a tumor cell.



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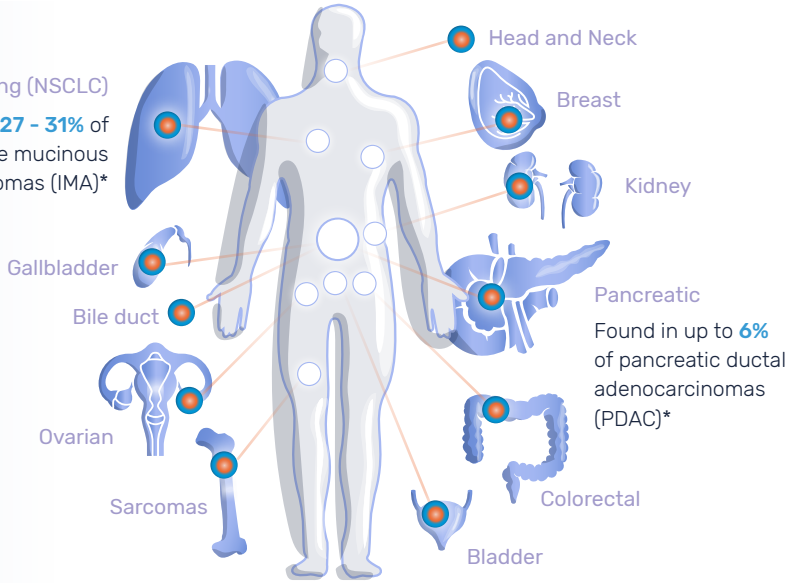
Though rare, NRG1 fusions are found across solid tumor types

0.2% Percent of solid tumors with an NRG1 fusion*

10+ Unique solid tumor types where an NRG1 fusion has been found

**Emerging research suggests that NRG1 fusions may be more common in some subtypes of cancer such as IMA (est. 0.2% of lung cancers) and PDAC (est. 90% of pancreatic cancers). As testing methodologies improve and more patients are tested, the identification of NRG1 fusions is expected to increase.*

SOLID TUMORS WITH IDENTIFIED NRG1 FUSIONS



New targeted therapies are needed for solid tumors with NRG1 fusions

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 or anti-PD-L1 therapies.

OS & DFS

Presence of an NRG1 fusion has been correlated with worse overall survival (OS) and disease-free survival (DFS) when treated with current therapies.

Therapy resistance

NRG1 fusions can also emerge at the time of progression and may be the driving cause of acquired resistance to a previous targeted therapy, such as an ALK, EGFR, or HER2 inhibitor.

THE CRESTONE APPROACH

Stopping the over-activation of HER3 with a targeted HER3 inhibitor like seribantumab may represent a precise treatment for tumors driven by an NRG1 fusion.

Because NRG1 fusions are found in multiple solid tumors and are likely to be a unique oncogenic driver alteration whenever they are found, we are now testing seribantumab in a "tumor-agnostic" way.

REFERENCES: Mota et al., Oncotarget. 2017; Fernandez-Cuesta et al., Clin Can Res. 2014; Drilon A et al., Cancer Discovery. 2018; Jonna et al., Clin Cancer Res. 2019; Jonna et al., Journal of Clinical Oncology 2020.; Jones MR et al., Clin Cancer Res. 2019; Duruisseaux M et al., ASCO 2019; Dimou A and Camidge DR, Clin Cancer Res. 2019; Moon SW et al., J Thorac Dis. 2018; Adamska A et al., Int J Mol Sci. 2017.