Incidence of Neurogulin (NRG1) gene fusions across tumor types

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Abstract

Neurogulin-1 (NRG1) encodes an EGF-like domain that can serve as a ligand for ErbB3 receptors.1, 2 NRG1 fusions can result in transmembrane proteins that bind ErbB3 and lead to heterodimerization with ErbB2 with subsequent activation of downstream signaling partners including PI3K, AKT, and NF-κB.3, 4 NRG1 fusions have been reported in a variety of tumors and multiple reports have evaluated responses to the irreversible pan-HER inhibitor afatinib and ErbB3 directed therapy.2, 5 The incidence of NRG1 fusions across tumor types is not established.

Methods

Tumor samples submitted for profiling between 01/16 - 04/18 at a CLIA-certified genomics laboratory (Caris Life Sciences, Phoenix, AZ) were assayed with anchored multiplex PCR for targeted RNA sequencing with the ArcherDX fusion assay (ArcherDx). Novel fusions and fusions with high reads (defined as ≥10% of total reads), high confidence after bioinformatics filtering, and considered in-frame, are included in this analysis.

Results

In total, 15,901 tumors successfully assayed, 32 cases (0.2%) harbored an NRG1 fusion. The incidence of NRG1 fusions varied by tumor type: 0.8% cholangiocarcinoma (2/257), 0.7% thyroid (1/134), 0.5% ovary (3/589), 0.4% pancreas (2/540), 0.3% NSCLC (20/6644), 0.2% breast (2/12,926), 0.2% sarcoma (1/489) and 1 case in sinonasal teratocarcinoma (SNTC). One of the 20 NSCLC cases (NRG1-SDC1) had squamous histology, the remaining were adenocarcinoma. No NRG1 fusions were detected in colorectal cancer (0/456) or glioblastoma multiforme (0/1335). In NSCLC, NRG1 fusions were mutually exclusive with oncogenic alterations in EGFR, ALK, ROS1, MET, and KRAS with the exception of one case that co-occurred with TP53/GCSC mutation.

Conclusion

Gene fusions in NRG1 can be identified in various tumor types, though the highest number of events was in NSCLC. Consistent detection of NRG1 fusions will need to account for multiple fusion partners. The optimal treatment of tumors harboring NRG1 fusions needs to be established.

References