Title: Incidence of *ERBB* gene fusions (*EGFR*, *ERBB2*, *ERBB4*) across tumor types

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Background: Gene fusions often represent critical therapeutic targets across cancer subtypes. Fusions within the ErbB family of receptor tyrosine kinases, including *EGFR*, *ERBB2* (*HER2*) and *ERBB4* (*HER4*), have been previously described and represent potentially actionable alterations. Here, we report the relative incidence and functional characterization of these rare genomic events.

Methods: Tumor samples (n=64,354; representing >40 tumors types) submitted to Caris Life Sciences (Phoenix, AZ) were molecularly profiled by next-generation sequencing of DNA (NextSeq, 592-gene panel; or NovaSeq, whole exome) and RNA (whole transcriptome). Gene fusion partners, in/out-of-frame status, retention of *ERBB* kinase domain, and topology of fusion breakpoints were characterized for each *ERBB* fusion transcript detected. Fusion prevalence was further examined in public data sets (TCGA, MSK-IMPACT and AACR GENIE).

Results: From the Caris database, a total of 64 *EGFR* fusion isoforms were detected in 59 tumors (incidence 0.09%); 83% were in-frame and 91% retained the *EGFR* kinase domain. 206 *ERBB2* fusion isoforms were detected in 114 tumors (0.18%); 37% were in-frame and 34% retained the *ERBB2* kinase domain. 131 *ERBB4* fusion isoforms were detected in 108 tumors (0.17%); 62% were in-frame and 51% retained the kinase domain. All fusions were detected at low incidence across all tumor types. *EGFR* fusions were most common in high grade glioma (1.7%, n=35), largely driven by recurrent *EGFR-SEPT14* fusions (n=20). *ERBB2* fusions were most common in esophageal/gastroesophageal junction carcinoma (1.1%, n=20), with recurrent fusion to *PGAP3* observed in multiple tumor types (n=37). *ERBB4* fusions were most common in ovarian (0.7%, n=40) and bladder (0.7%, n=15) cancers, which often resulted from recurrent fusion with *IKZF2* (n=36). *EGFR* and *ERBB2* fusions were generated predominantly (44-48%) from inversion events, while *ERBB4* fusions arose more frequently and at similar rates (27-32%) from deletions, duplications, or translocations. Mining of public data sets corroborated the prevalence of *ERBB* gene fusions: the frequency of *EGFR* fusions was 0.63%, *ERBB2* was 0.14% and *ERBB4* was 0.04%. *TP53* mutations frequently co-occurred with *ERBB2* and *ERBB4* fusions (>60% average across public data sets), with higher co-mutation rates (>70%) observed for samples in the Caris database.

Conclusions: *ERBB* gene fusions are detectable at low frequency in various tumor types and may represent a unique genomic subset of cancer. Identification of novel *ERBB* gene fusions warrants further investigation to determine the potential pathogenicity and actionability of these fusions.