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

Laura Schubert¹, Andrew Elliott², Robert Doebele³, Emil Lou⁴, Hossein Borghaei⁵, Michael Demeure⁶, Razelle Kurzrock⁷, Anh Le¹, Joshua Reuss⁸, Ignatius Ou⁹, David Braxton⁶, Christian Thomas¹⁰, Sourat Darabi⁶, Michael Korn¹¹, Wafik El-Deiry¹², Stephen V. Liu⁸

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.