ERBB2 (HER2) Mutation Spectrum in Solid Tumors

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Introduction/Background

The ERBB2 gene (Fig1) which encodes for Her2 is a major proliferative driver for several cancer types. Gene amplification and protein expression are associated with sensitivity to Her2-targeting drugs. In some cancer types ERBB2 mutations may be more relevant in carcinogenesis than gene amplification or protein expression. The mutation spectrum of ERBB2 in solid tumors is relatively unknown. The emergence of NGS methodology had enabled high throughput detection of both known and novel oncogenic mutations in human genome including the presence of activating mutations of ERBB2.

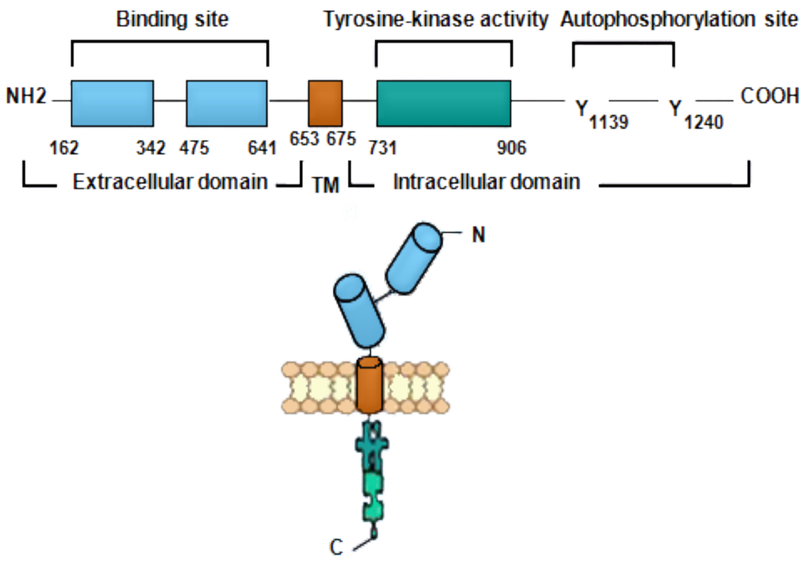

Figure 1 – ERBB2 structure

Materials and Methods

Comprehensive genomic profiling was performed on tumors from 7497 cancer patients including 850 breast, 770 colorectal (CRC), 910 lung (NSCLC), 823 uterine/cervical, 1372 ovarian and 297 pancreatic cancers. We also profiled 323 melanoma and 2152 other solid tumors (e.g. glioblastomas, sarcomas, bladder carcinomas). Direct sequence analysis of ERBB2 was performed on genomic DNA isolated from a formalin-fixed paraffin-embedded tumor sample using the illumina MiSeq platform. Specific regions of the genome were amplified using the illumina TruSeq Amplicon Cancer Panel. The Her2 protein expression and gene copy numbers were determined by immunohistochemistry and dual in situ hybridization (dual ISH), respectively (Ventana Medical Systems).

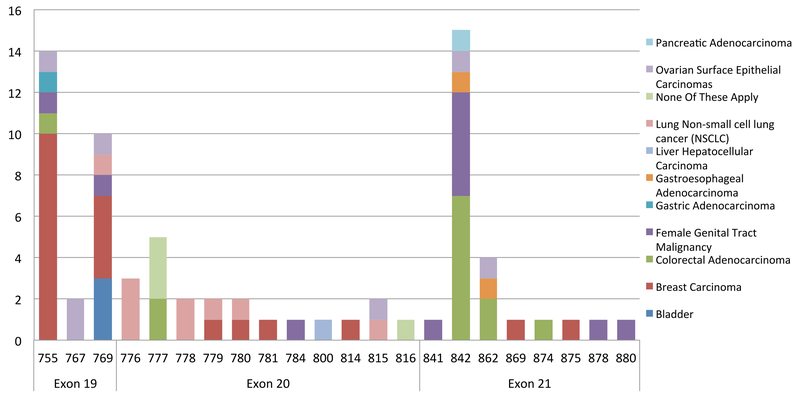

Figure 2 – ERBB2 (Her2) Mutation Spectrum in solid tumors

Results

ERBB2 mutations in the kinase domain were detected in 69 patients (1% of all cases; Fig 2). These include previously published activating mutations (G776delinsVC, P780_Y781insGSP, V842I, L755S, V777L, D769Y) and several novel ones (such as I767F, R784C). 12 cases with coexisting HER2 amplification included: D769Y(breast and ovary) and L755S (breast), D769H (bladder), T862A (ovary and esophagus), and two cases with V777L (CRC). 53 of the 69 patients also had additional gene mutations (e.g. TP53, APC, PIK3CA, PTEN, KRAS). 16(23%) patients had ERBB2 mutation identified as the sole driver mutation, including L755S in CRC, breast and ovarian cancer, D769H in bladder cancer, G776delinsVC and D769E in NSCLC.

Conclusions

1. ERBB2 mutation might be the sole identified driver mutation in various solid tumors including breast, ovarian, CRC, NSCLC.
2. Activating ERBB2 mutation can coexist with ERBB2 gene amplification and/or with mutations in various other key driver genes.
3. The effectiveness of targeted anti-Her2 therapies in non-amplified ERBB2 mutated cancers which do not over-express the protein needs to be established.

**This abstract contains updated information since original submission.*