FGFR2: A Pan-Genomic Target

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ABSTRACT

Background: *FGFR2* genomic alterations (GA) have been described in a variety of solid tumors and emerged as biomarkers for investigational agents undergoing clinical trials

Results: *FGFR2* GA were detected in 2,993 (1.5%) cases featuring short variant (SV) mutations (42%), copy number changes (27%), rearrangements/fusions (28%) and multiple GA (3%). The most frequent SV GA were S252W, N549K, C382R, P253R, Y375C, K659E and R664W. A small cohort (2%) of tumors featured the V564I and V564L GA that are associated with resistance to TKI drugs. The *FGFR2*-altered cases were 69% female/31% male with median age of 61 yrs. Most frequent GA in *FGFR2* altered cancers: *TP53* (47%), *PIK3CA* (22%), *PTEN* (20%), *ARID1A* (18%), *CDKN2A/2B* (18/14%) and *MYC* (12%). FGFR2 SVs most common in endometrial, breast carcinomas (ca) and CUP. *FGFR2* amplification most common in breast, gastroesophageal and lung ca. *FGFR2* rearrangement/fusions most common in cholangioca (37% of rearrangement positive cases), CUP (15%), pancreatobiliary (12%) and breast ca (6%). The *FGFR2-BICC1* was the most frequent fusion followed by fusions with *TACC2*, *AHCYL1*, *CCDC6*, *VCL*, and *KIAA1217*. MSI-High status present in 6.8% of evaluable *FGFR2* altered cases (63% in endometrial ca). Median TMB was 3.5 mut/Mb with 21.8% featuring ≥ 10 mut/Mb and 12.0% featuring ≥ 20 mut/Mb. Only 63% of MSI-High *FGFR2* altered tumors had TMB ≥ 20 mut/Mb. 12.7% *FGFR2* altered had > 1% PD-L1 staining with 3.4% > 50% staining. 29% of PD-L1 IHC+ cases in NSCLC. *FGFR2* altered ca's responding to anti-FGFR2 therapies will be presented.

Conclusions: *FGFR2* GA are most frequent in cholangioca, breast, GI tract, lung ca and CUP, with enrichment of *FGFR2* fusions in biliary tract ca. Cases with *FGFR2* GA typically do not feature other kinase driver GA and are associated with mutations in the MTOR/PIK3CA/AKT pathways. Finally, in contrast with RTK driver GA in *EGFR* (5.7%) and *ERBB2* (7.9%), at 12.0%, across all tumor types, *FGFR2* mut cancers may have higher frequency of TMB ≥ 20 mut/Mb suggesting potential immunotherapy responsiveness

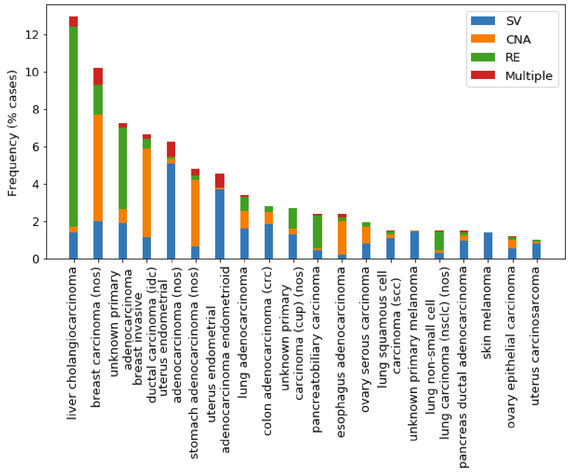
MATERIALS AND METHODS

- ≥50 ng DNA extracted from 40 µm of FFPE sections
- Sequencing performed for up to 315 cancer-related genes and introns from 28 genes commonly rearranged in cancer
- Hybrid capture-based sequencing using adaptor ligation-based libraries
- Mean coverage depth >550X
- Base substitutions, insertions and deletions (short variants; SV), rearrangements, and copy number changes were assessed
- Tumor mutational burden (TMB) calculated from 0.83-1.14 Mb sequenced DNA
- PD-L1 expression was determined by IHC (predominantly Dako 22C3 antibody).

1. Frampton GM, Fichtenholtz A, Otto GA, et al. Nat Biotechnol. 2013;31:1023-1031
2. Chalmers ZR, Connelly CF, Fabrizio D. Genome Med. 2017;19;9:34

RESULTS

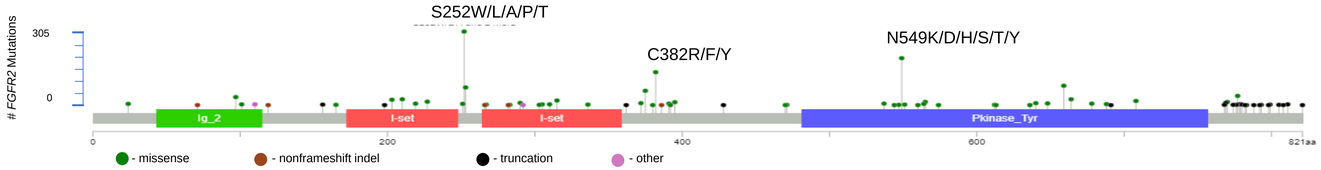
Figure 1. Distribution of *FGFR2* Alterations by Tumor Type



- *FGFR2* GA are seen across more than 50 disease types, with enrichment in liver cholangiocarcinoma as well as breast and uterine carcinomas
- Frequency of specific classes of *FGFR2* alteration types vary widely by tumor type

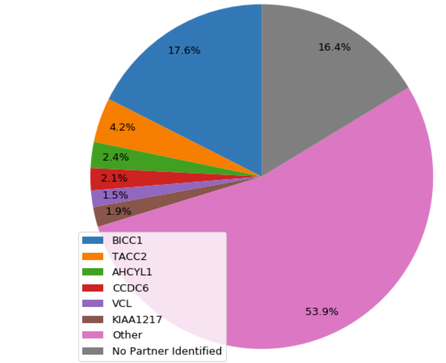
- *FGFR2* rearrangements co-occur with a variety of distinct partners, with recurrent partners accounting for >33% of all rearrangements
- Most recurrent fusions include *FGFR2* exons 1-17, which retain the kinase domain and are predicted to be activating

Figure 3. Lollipop Plot of All *FGFR2* Mutations Across Tumor Types



- Missense mutations are seen across *FGFR2* with hotspots at S252, C382R, and N549
- Truncations are primarily observed in the C-terminus of *FGFR2* after the kinase domain

Figure 2. Distribution of Partners in *FGFR2* Rearrangements and Schematic of 10 Most Common Fusions



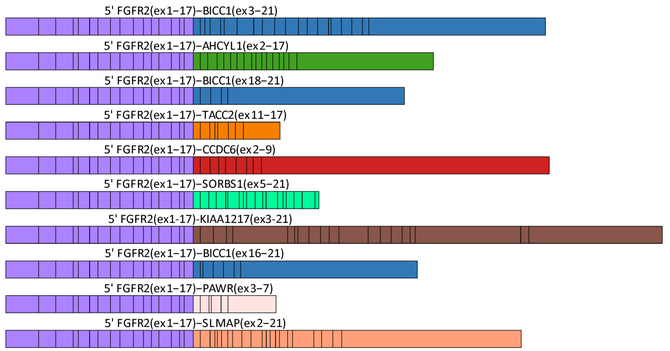
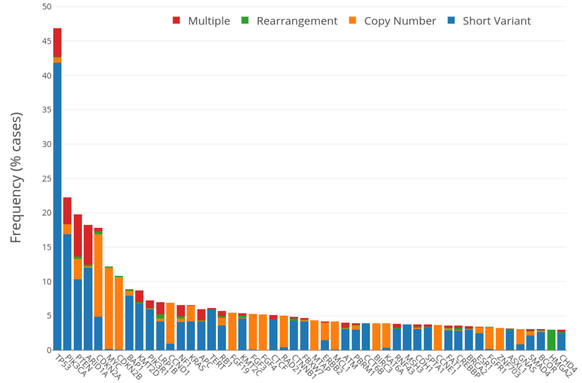


Figure 4. Long Tail Plot of Genomic Alterations in *FGFR2* Altered Tumors



- Alterations in PI3K/AKT/mTOR pathway commonly co-occur with *FGFR2* alterations
- Alterations to other kinases, such as *ALK, EGFR,* and *ERBB2* rarely co-occur with *FGFR2* alterations

CONCLUSIONS

- Diverse *FGFR2* alterations are detected in 1.5% of all cancers, and are most frequent in cholangio, breast, GI tract, lung and unknown primary carcinomas, with enrichment of FGFR2 fusions in biliary tract carcinomas
- All classes for *FGFR2* alterations were represented including point mutations and indels (42%), amplification (27%), rearrangements (28%), and multiple alterations (3%)
- *FGFR2* rearrangements were found across multiple tumor types and recurrent *fusion* partners accounted for only ~1/3 of rearrangements
- FGFR2 alterations are typically mutually exclusive with other kinase drivers, but co-occur with alterations in the MTOR/PI3K/AKT pathways
- Comprehensive genomic profiling to detect diverse *FGFR2* alterations across cancer types is necessary to match patients with active clinical trials of FGFR inhibitors