Co-occurrence of gene fusions with SNV/Indels and with CNVs on solid tumors in a cohort of 795 patients from the community setting

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Background:

Co-occurrence of gene alterations often plays a relevant role in the selection of potential targeted therapies for a cancer patient. It has been reported that patients with fusions respond to fusion-targeted therapy regardless of the tissue type. Less is known about the co-occurrence of SNVs and Indels with gene fusions and copy number variation.

Methods:

Data from 795 patients tested with a CGP assay that interrogated SNVs/Indels on 517 genes, fusions of 59 genes, and CNV on 55 genes were included in the study. Variant clinical significance was determined as described by the FDA-recognized OncoKB database or the National Comprehensive Cancer Network, NCCN. The study was performed with an IRB approved research protocol.

Results:

We examined the co-occurrence of copy number variation, RNAseq fusion detection, and actionable SNV and Indel mutations in community care settings to understand their combined potential clinical implications. We analyzed the co-occurrence of fusion events with targetable mutations, the overlap of fusions with copy number variation detection, and simultaneous copy number variation and actionable SNV/Indels. Roughly 5.3% (38/ 713) of cases with pathogenic/likely pathogenic OncoKB gene mutation also had a fusion event. Conversely, 80.9% (38/47) of patients harboring a gene fusion had pathogenic OncoKB mutation(s). When analyzed alone, amongst the 40 fusions, the most frequent were SDCCAG8::AKT3 (12%), TMPRSS2::ERG (10%), ESR1::CCDC170 (7%), and ROS1 fusions (n=6). Fifteen (15) of these fusions have potentially actionable significance as defined by NCCN and/or OncoKB database. ROS1 fusions most commonly had TP53 mutations (66.66%), with equal detection of other pathogenic OncoKB co-mutations in BRCA2, EGFR, and BRAF. Meanwhile, 6 of the patients had PIK3CA oncogenic mutations with an available therapeutic selection, and 2 had a fusion that offers additional clinical implications. Additionally, ESR1 was the most frequent fusion partner with PIK3CA co-mutation with OncoKB described actionability. The most common SNV/Indel mutation observed was TP53, with 31 unique tumors bearing co-occurring TP53 mutation with a fusion. In addition, 36.2% (17/47) of fusion-positive tumors had concurrent copy number variation, whereas 6.9% (17/245) of tumors with copy number alteration detection (n=245) concurrently had a fusion. Moreover, 32.0% (228/713) of samples with pathogenic gene mutation also had copy number variation(s). Conversely, 93.1% (228/245) of tumors with copy number variation had pathogenic OncoKB mutation.

Primary site of Samples with Co-Occurring Fusion & CNV Detection

Bladder/Urinary Tract	CNS/Brain	Other
Bowel	Esophagus/Stomach	Ovary/Fallopian Tube
Breast	Lung	Skin

Comprehensive testing captures each patient's full actionable profile

- Gene fusion detection can override SNV and Indel therapies and expand therapeutic selection
- Comprehensive testing enhances the chances of identifying markers for clinical trials, especially for stage III/IV and therapy-resistant cancers.

Keywords: Clinically actionable, tumor agnostic, Real World Data, NGS comprehensive testing

Data:

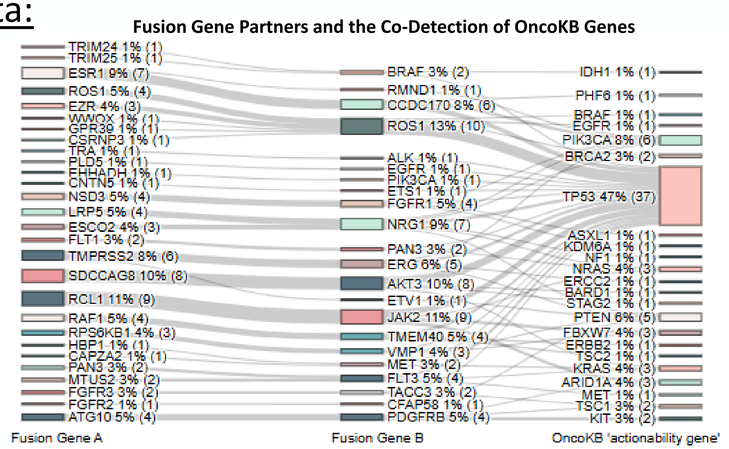

Figure 1. Relationship of fusion partners and cooccurrence of actionable, pathogenic/likely pathogenic SNV/Indels

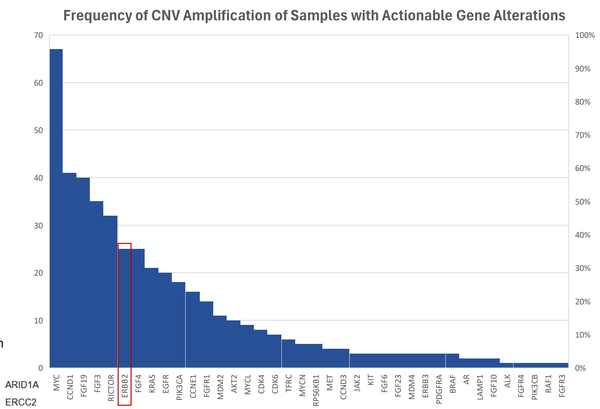

Figure 3. Frequency of copy number gene amplification across samples with both copy number variation and OncoKB described actionable genes; where 32.0% of samples with pathogenic/likely pathogenic OncoKB gene mutation (713) had co-detection of copy number variation(s)(228).

Conclusion:

Genomic rearrangements, albeit relatively infrequent, can often be concomitantly expressed in the context of other actionable DNA mutations or CNVs, which can lead to improved understanding of tumorigenesis and improve clinical care as tumors are tested with comprehensive genomic profiling assays.

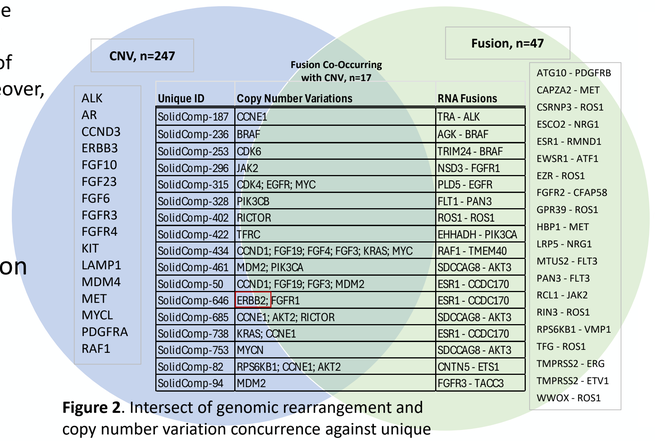

Figure 2. Intersect of genomic rearrangement and copy number variation concurrence against unique detection.

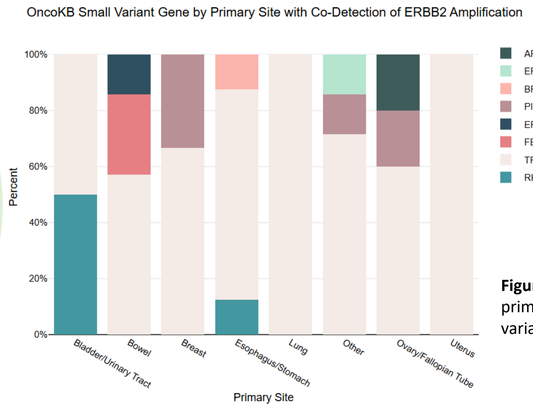

Figure 4. SNV/Indel and ERBB2 amplification detection across different primary tumor sites. *Note:* ERBB2 amplification is the only copy number variant with FDA Level 1 Approved therapeutic treatment.

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Reference: https://www.oncokb.org/actionable-genes (166 actionable genes)
OncoKB™: Suehnholz et al., Cancer Discovery 2023 and Chakravarty et al., JCO PO 2017.