457P - Circulating tumor DNA from patients with advanced colorectal cancer is enriched for EGFR extracellular domain mutations

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BACKGROUND

Comprehensive genomic profiling (**CGP**) of plasma circulating tumor DNA (**ctDNA**) provides a minimally invasive method to profile advanced colorectal cancer (**CRC**). The landscape of genomic alterations in CRC using ctDNA-based CGP was compared to tissue based CGP.

METHODS

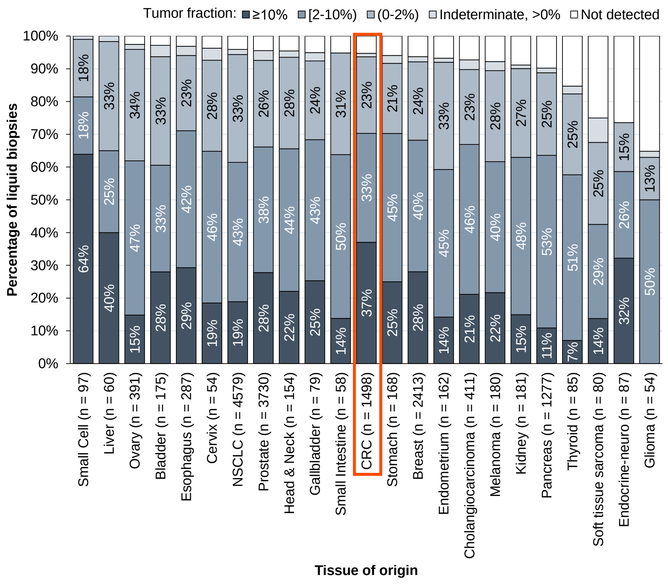
Plasma from 1,498 patients (**pts**) with CRC was analyzed using FoundationOne® Liquid CDx and compared with 27,931 CRC FoundationOne® CDx tissue biopsy results (11,406 were from metastatic sites or lymph nodes). In 271 pts with both specimens, positive percent agreement (**PPA**) was calculated at the variant level, with tissue as reference. Tumor fraction (**TF**) was estimated using a measure of aneuploidy; variant germline status was computationally predicted.

RESULTS

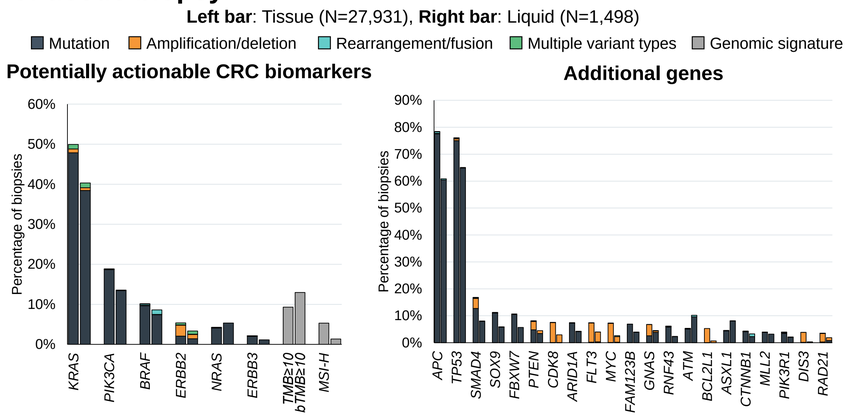
CRC plasma biopsies tend to contain high levels of ctDNA

Of 1,498 pts with CRC:

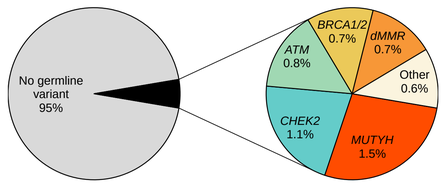
- 1,419 (95%) had detectable ctDNA
- 1,053 (70%) had tumor fraction ≥2%
- 555 (37%) had tumor fraction ≥10%



Genomic landscape detected in ctDNA largely resembles that of tissue biopsy



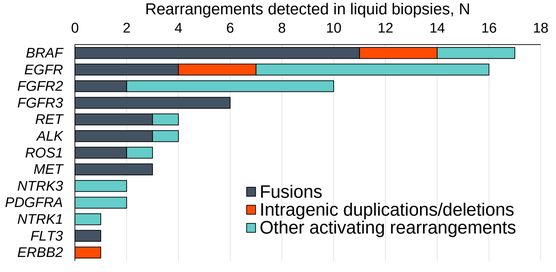
ctDNA detection of suspected germline variants



Detection of suspected germline variants (in 24 genes eligible for the F1LCDx germline banner). The most frequent germline variants were detected in: *MUTYH* (22 pts), *CHEK2* (17 pts), *ATM* (12 pts), *MLH1/MSH2/MSH6/PMS2* (10 pts), and *BRCA1/2* (10 pts).

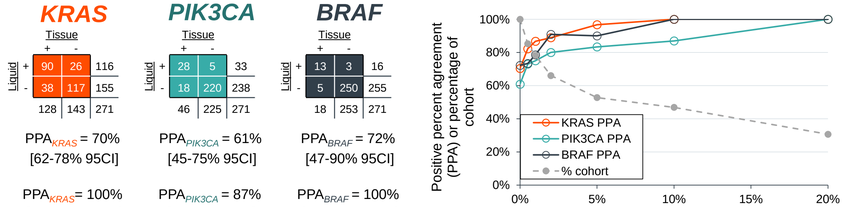
ctDNA detection of activating rearrangements

Breakpoints detected in Introns:	Exons:
1,3,7,8,9,10,17	8
7,24,25,27	17,25,26
17	
8,17,18	
11	3
17,19	
32,35	
3,9,13	
14	
11	
	11
11	
15	16

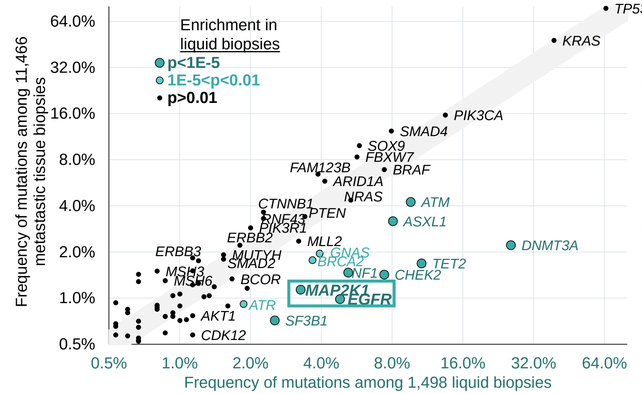


Concordance between tissue and liquid biopsies

Liquid and tissue CGP results from 271 pts used for concordance analysis (median collection time difference: 12 months).
PPA for ctDNA detection of KRAS, PIK3CA, and BRAF mutations increases in samples with higher ctDNA fraction.



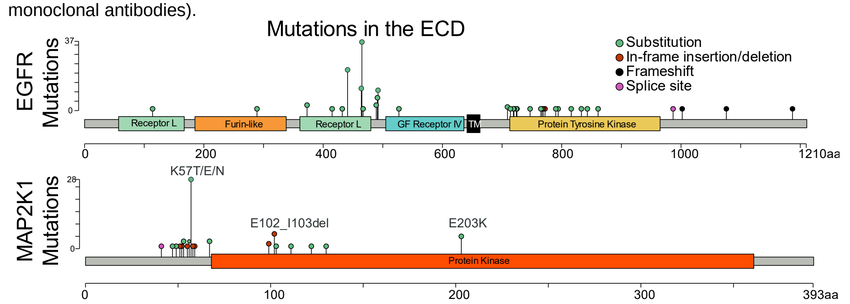
Enrichment of EGFR inhibitor resistance mutations in ctDNA

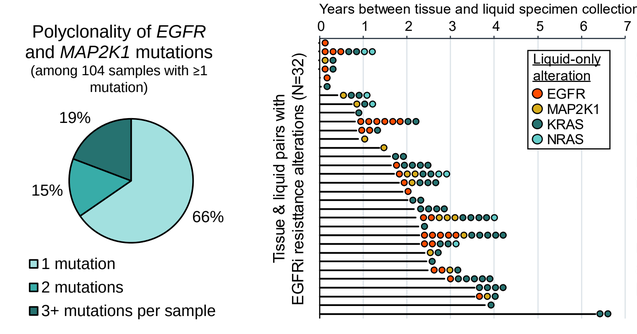


A comparison of metastatic tissue biopsies to liquid biopsies revealed significant enrichment in mutations that drive clonal hematopoiesis (*DNMT3A, TET2, SF3B1*) as well as mutations associated with acquired resistance to EGFR inhibitors (*EGFR, MAP2K1*).

EGFR inhibitor resistance in CRC liquid biopsies

Many EGFR mutations detected in liquid were in the extracellular domain (resistance to EGFR-directed monoclonal antibodies).





EGFR and *MAP2K1* mutations were detected polyclonally in some liquid biopsies.

In paired analysis, EGFRi resistance alterations exclusive to liquid biopsy were detected in 32 tissue/liquid pairs. These mutations may reflect resistance acquired over time and/or preexisting tumor heterogeneity.

Conclusions

CGP of plasma from patients with CRC contains rich ctDNA signal and recapitulates the genomic landscape detected in tissue biopsies. ctDNA-based detection of *KRAS* and *BRAF* alterations, targetable fusions, and possible resistance mutations, suggests this may be a compelling alternative to tissue CGP when a tissue specimen is inadequate or unavailable.