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Abstract 616: Blood-based molecular landscapes of resistance to EGFR blockade in colorectal cancer patients

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Abstract

The molecular landscape of colorectal cancers (CRC) is presently assessed by genotyping neoplastic tissue obtained through surgical or bioptic procedures. We evaluated whether blood-based molecular profiles could be used to perform diagnostic determinations and monitor resistance to therapy in colorectal cancer patients. We find that RAS pathway mutations, which are commonly evaluated prior to administration of anti-EGFR antibodies, can be ascertained directly in the blood. Sequencing of circulating DNA identified genomic alterations in KRAS, NRAS, MET, ERBB2, FLT3, and MEK1 in patients with primary or acquired resistance to cetuximab or panitumumab. Secondary resistance to EGFR blockade is frequently accompanied by emergence of mutant RAS clones, which can be tracked in blood. We find that upon withdrawal of anti-EGFR antibodies, KRAS alleles decline in circulating DNA indicating that clonal evolution continues beyond clinical progression. Functional analysis of CRC cell populations, which had acquired resistance to cetuximab, revealed that KRAS mutant clones can decay when EGFR blockade is suspended. These results establish proof of principle that genotyping colorectal cancers using circulating DNA can inform therapeutic decisions, identify mechanisms of drug resistance and provide insights for further lines of therapy.

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