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Abstract 2848: Radiographic and genomic evolution of individual metastases during HER2 blockade in colorectal cancer

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Abstract

Targeting HER2 with trastuzumab and lapatinib is effective in ERBB2 amplified metastatic colorectal cancer (mCRC). Although at least 30% of the patients initially respond, secondary resistance occurs in most of the cases.

Since the drivers of secondary resistance to trastuzumab and lapatinib in ERBB2 amplified mCRC are unknown, we exploited longitudinal plasma collections and patient-derived cell models to define the molecular bases of resistance to HER2 blockade. Levels of ERBB2 amplification in plasma circulating tumor DNA (ctDNA) paralleled response and relapse. The emergence of EGFR, ERBB2, RAS, BRAF and PIK3CA variants in ctDNA was associated with resistance. Radiographic measurements of individual metastases coupled with longitudinal liquid biopsies unveiled lesion-specific patterns of heterogeneous response in several patients. Phylogenetic tracking and functional analyses on tissue samples and patient-derived cell models established from eight metastases of a single case revealed new druggable oncogenic dependencies and genomic evolution associated with resistance. These data highlight the relevance of coupling imaging and liquid biopsies analyses in precision oncology and provide the rationale for additional lines of therapies in HER2 positive mCRC relapsing upon HER2 blockade.

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