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SO-23 The genomic temporal heterogeneity of circulating tumor DNA in metastatic colorectal cancer under first-line treatment

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Background: The treatment strategies of metastatic colorectal cancer (mCRC) develop as molecular diagnostics improve, the failure of first and later lines of therapy may be caused by the molecular heterogeneity within patients over time. Circulating tumor DNA (ctDNA) sequencing is increasingly utilized in the clinical management of patients with colorectal cancer. However, the dynamic change in plasma genetic mutations during treatments and its impact on clinical outcomes remains largely unknown.

Methods: 223 patients with mCRC under first-line treatment between April 2018 and January 2020 in Sun Yat-sen University Cancer Center were enrolled (NCT228614). Patient plasma samples, with or without tumor samples, were sequentially collected at baseline and every 6-8 weeks with response evaluation before and until disease progression. Somatic mutations were detected in ctDNA using the panel HapOncoCDx, which includes 378 cancer-related genes. Whole-exome sequencing of tumor samples was performed with HapOncoCDx WesPLus.

Results: The genomic alterations in paired baseline tissue and plasma samples from 109 patients displayed a favorable concordance (78.0%, 85/109). After a period of first-line treatment (median 4.9 months), 45.2% (33/73) of RAS-mutant patients showed RAS mutations clearance and 54.5% (6/11) of BRAF-mutant patients showed BRAF mutations clearance, while 4.1% (5/123) and 0.5% (1/185) of patients gained new RAS or BRAF mutations in ctDNA. Unlike RAS and BRAF, ERBB2 amplification, NTRK fusion and other actionable targets for clinical trials, including KRAS p.12C, PTEN, NF1, MTOR, MET, CDK12, CDKN2A and FGFR1/2/3, remained consistent over time in most patients. Patients with plasma RAS or BRAF clearance showed similar progression-free survival (PFS) and overall survival (OS) with patients who remained RAS wild-type [median PFS (mPFS) = 15.5 vs 13.8 months, P = 0.827; median OS (mOS) = not reached (NR) vs NR, P = 0 .483] or BRAF wild-type (mPFS = 20.2 vs 12.7 months, P = 0.339; mOS = NR vs 31.4 months, P = 0.572), while much better outcomes than those who remained RAS mutant (mPFS = 15.5 vs 6.7 months, P < 0.001; mOS = NR vs 15.5 months, P < 0.001) or BRAF mutant (mPFS = 20.2 vs 6.4 months, P = 0.001; mOS = NR vs 11.4 months, P = 0.012). In contrast, patients who gained new RAS or BRAF mutations showed similar prognosis with those who remained RAS or BRAF mutant, while numerically shorter PFS and OS than those who remained RAS wild-type (mPFS = 7.0 vs 13.8 months, P = 0.133; mOS = 15.0 months vs NR, P < 0.001) or BRAF wild-type (mPFS = 8.7 vs 12.7 months, P = 0.121; mOS = NR vs 31.4 months, P = 0.997).

Conclusions: This prospective, serial and large-scale ctDNA profiling study reveals the temporal heterogeneity of mCRC-related somatic variants, which should be given special attention in clinical practice, as evidenced by the finding that the shift in RAS/BRAF mutational status can yield a drastic change in survival outcomes.

Clinical trial identification: NCT228614.

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