

Meeting Abstract: 2013 ASCO Annual Meeting I

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Massively parallel sequencing (MPS) of circulating DNA in patients with metastatic colorectal cancer (mCRC): Prognostic significance and early changes during chemotherapy (CT).

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Abstract

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Background: Prognostic and predictive biomarkers in mCRC are urgently needed. Circulating tumor cells are a promising blood biomarker, but are detectable in only a minority of pts. Recently, analysis of circulating tumor DNA (ctDNA) has shown promise as a liquid biopsy, reflecting the evolving mutational status of the tumor. Here we explored baseline ctDNA as a prognostic marker, and early changes in ctDNA as a marker of CT response. **Methods:** Serial plasma samples and CEA were collected at baseline (D1), day 3 (D3) and cycle 2 day 1 (C2D1) from 40 mCRC pts receiving standard combination CT. Restaging scans performed at 8 weeks were centrally assessed using RECIST criteria. Samples were analyzed at Johns Hopkins Kimmel Cancer Center. Initially tumor tissue was analyzed for hotspot mutations in *TP53*, *APC*, *KRAS*, *BRAF*, *PIK3CA* and *FBXW7*. The same mutation was queried and quantified in plasma using a MPS platform (Safe SeqS). Log rank test was used to compare survival curves and Wilcoxon matched pairs test was used to compare paired plasma samples. **Results:** Preliminary data is available on 19 pts in this ongoing study. Using our initial panel at least 1 mutation was found in 16 of 19 (84.2%) tumors (7 *KRAS*, 3 *TP53*, 3 *BRAF*, 2 *APC* and 1 *PIK3CA*), with matching ctDNA found for each pt. For the remaining 3 cases a further panel of mutations is being analyzed. Median D1 cell free DNA (cfDNA) and ctDNA levels were 1.98 ng/ul (0.15 – 57.18) and 523 mutant fragments (frag)/ml (0.4 – 109,876), respectively. Pts with D1 cfDNA of ≥ 2.5 compared with < 2.5 had shorter median overall survival (OS; 6.9 v 12.2 months, $p = 0.0086$), with a trend for shorter progression free survival (PFS; 3.6 v 8.2 months, $p = 0.3477$). A surge of ctDNA level from D1 to D3 was typically observed (median increase: 91.2 frag/ml, $p = 0.0313$), followed by a drop (median decrease from D1 to C2D1: 208.8 frag/ml, $p = 0.0098$). All pts with a decrease in ctDNA at C2D1 had a reduction in tumor size at 8 weeks. **Conclusions:** In all cases of mCRC where tumor mutation was identified,

matching ctDNA was detected in plasma. Circulating DNA is a promising marker of prognosis. Early changes in DNA levels may be a useful marker of tumor response.

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