MRD residual disease detection and tracking tumor evolution using ctDNA in stage I-III colorectal cancer patients

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European Society of Medical Oncology | Virtual Meeting | September 19 - 21, 2020 #3826

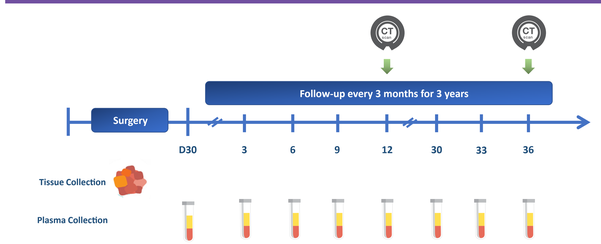
Background

- Patients with colorectal cancer (CRC) possess a high degree of tumor spatial heterogeneity.[1] At diagnosis, ~25% of colorectal cancer (CRC) patients have synchronous metastases, and ~30% develop metachronous metastases[2]
- Little is known about the heterogeneity of these tumors, which warrants better identification tools to detect recurrence.
- Heterogeneous tumors undergo clonal genomic evolution over time in response to selective pressures[3]
- In this study, we sought to evaluate the clinical utility of circulating tumor DNA (ctDNA) in identifying minimal residual disease (MRD) and recurrence monitoring.

Methods

- This is a prospective, multicenter cohort study, which recruited patients (n = 196) diagnosed with stage I-III CRC. Median follow-up time was 21.9 (1.4 - 41.9) months.
- For each patient, a personalized and tumor-informed, Signatera™ bespoke multiplex-PCR, NGS assay was used to track ctDNA in plasma samples at clinically relevant time points throughout the duration of the study (**Figure 1**).
- The relationship between ctDNA status and the clinical outcomes were evaluated. For a subset of patients (n = 6), comparison of primary and metastatic tumors was performed to determine the phylogenetic evolution **(Figure 2A)**. Separately, for another subset of patients (n = 5), the mutational profiles of synchronous tumors were compared to understand the presence of common mutations **(Figure 2B)**.

Figure 1. Study Design



Synchronous CRC tumors are genetically unrelated and require individual assays for ctDNA detection. Post-operative MRD status and longitudinal monitoring using ctDNA can detect patients with a high risk of recurrence and guide treatment decisions.

Figure 2. Comparison of Signatera Assays in Primary and Synchronous Tumors

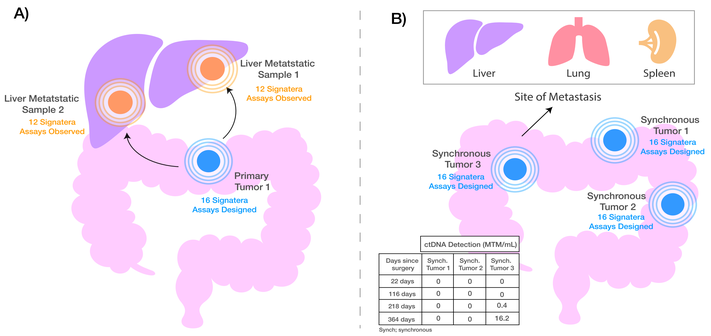


Figure 2. (A) Comparison between primary and metastatic tumors showed phylogenetic similarity with at least 50% overlap (50-80%) with majority of the Signatera assays (prioritizes clonal variants) having common variants between the two tumor types. **(B)** Conversely, synchronous tumor analysis showed no similarity between variants, indicating distinct mutational profiles. Of the 5 patients only 1 patient experienced relapse. This patient is exemplified with three synchronous tumors. Plasma analysis revealed, that only the Signatera assays for one of the synchronous tumors (#3) detected post-operative ctDNA and disease recurrence.

Figure 3. Relapse-Risk Stratification by ctDNA Status

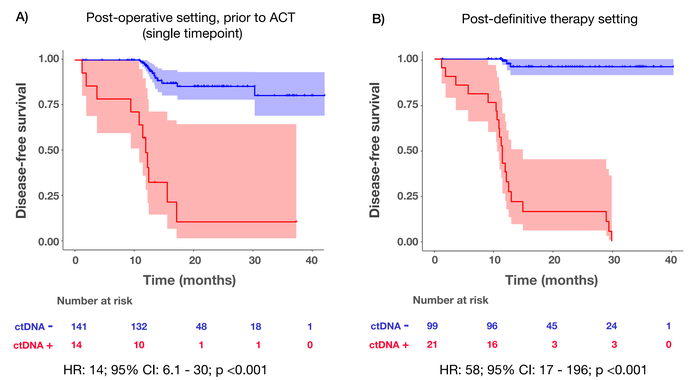


Figure 3. Relapse-Risk Stratification by ctDNA Status: **(A)** In post-operative setting (single time point: prior to ACT, 9% (14/155) of patients showed MRD-positivity, and 78.5% (11/14) relapsed (HR: 14; 95% CI: 6.1-30; p<0.001). **(B)** In Post-definitive treatment setting a shift to ctDNA-positivity during longitudinal monitoring (n=120) was associated with poor clinical outcome (HR: 58, 95% CI: 17-196; p<0.001).

Table 1. Multivariable Analysis of ctDNA Status as a Prognostic Factor for RFS

N=120 Events= 23	Hazard Ratio	Confidence Interval (95%)	Pr(>|z|)
ctDNA status (ref. negative)	57.71	16.97 - 196.40	<0.001

Table 1. Multivariable analysis showed longitudinal ctDNA positivity to be the only significant prognostic factor associated with inferior RFS. Multivariable analysis included: ctDNA status, age, sex, stage, MSI, perineural invasion, and the number of resected lymph nodes. ctDNA biomarker was found to have the highest effect size for prognosis in patients with stage II/III CRC.

Figure 4. Detection of Recurrence: ctDNA vs. Radiologic Imaging

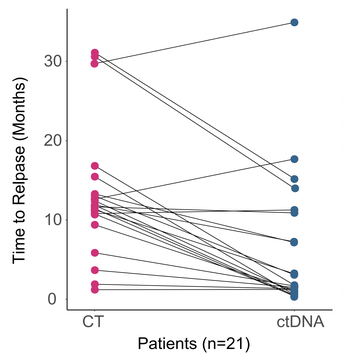


Figure 4. The median time from ctDNA detection by serial ctDNA analyses to radiologic relapse was 8.1 months (range, 0.6 - 16.6 months).

The sensitivity and specificity of longitudinal ctDNA analyses were 87.5% (21/24) and 99.1% (121/122), respectively.

Acknowledgments and Disclosures

A.C. would like to acknowledge research funding from Genentech, Merck Serono, Roche, Beigene, Bayer, Servier, Lilly, Novartis, Takeda, Astelas, Pierre Fabre, Fibrogen, Amcure, Sierra Oncology, Astra Zeneca, Medimmune, BMS, MSD; consultancy/advisory board: Merck Serono, Roche, Beigene, Bayer, Servier, Lilly, Novartis, Takeda, Astelas; speaking: Merck Serono, Roche, Amgen, Bayer, Servier, Foundation Medicine; grant support: Merck Serono, Roche; Executive Board member of ESMO, Chair of Education ESMO, ESMO Education Director, INCLIVA General and Scientific Director, Associate Editor: Annals of Oncology and ESMO Open, Editor in chief: Cancer Treatment Reviews. N.T. would like to acknowledge research funding from Mutua Madrileña; Speaking: Servier, Amgen. S.S., H.W., S.S., A.S.T., H.S., B.Z. and A.A., are employees of Natera, Inc. with stock/options to own stock in the company. All other authors do not have any conflict if interest. Editorial/poster development support was provided by Allyson Malashevich, PhD and Meenakshi Malhotra PhD from Natera, Inc.

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