A multicenter study to evaluate the impact of circulating tumor DNA guided therapy (BESPOKE) in patients with stage II and III colorectal cancer

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Background

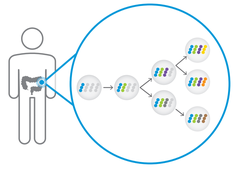
- Colorectal cancer (CRC) is the fourth most common cancer and the second leading cause of cancer-related death in the U.S.[1]
  - The standard of care for Stage II and III CRC patients includes surgical resection of the primary tumor, followed by adjuvant chemotherapy (ACT) in high risk patients to avoid the risk of recurrence
  - Current biomarkers show limited clinical utility in detecting **minimal/molecular residual disease** (MRD) post-resection and in **monitoring recurrence** in patients with high risk stage II/III CRC
  - An urgent need exists to develop biomarkers for high risk stage II/III CRC patients that show improved clinical utility to better guide ACT treatment decisions.
- Personalized ctDNA testing provides sensitive, specific, and dynamic detection of MRD post-resection, as well as early detection of recurrence during surveillance, up to 16.5 months ahead of radiological imaging (average 8.7 months) in patients with CRC[2]
  - ctDNA can be used to identify MRD-negative patients that have already benefited from surgery/definitive therapy and may avoid unnecessary ACT and its associated side-effects/toxicity
  - ctDNA also allows for consideration and/or intensification of systemic treatment for MRD-positive patients, who ideally need 'adjuvant' therapy to avoid relapse
  - Early detection of MRD using a personalized, tumor-informed ctDNA assay provides a unique opportunity to identify optimal treatment options for patients, which can in turn, result in improved survival and quality of life in CRC survivors
- This trial is designed to evaluate the ability of the bespoke ctDNA test to inform Stage II/III CRC ACT treatment decisions and aid in monitoring MRD status, clearance, and recurrence.

Study Design

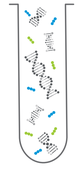
- The study is a prospective, multicenter clinical trial with a historical control arm, that utilizes a personalized ctDNA assay (Signatera™ bespoke mPCR NGS), designed to track tumor-specific mutations in patients with stage II/III CRC for MRD determination and recurrence monitoring **(Figure 1)**.
- A total of 1,000 patients will be enrolled at >50 US sites and will be followed for up to 2 years with periodic blood collection, timed with the standard-of-care visits (post-operative/surgery visit, prior to initiation of systemic chemotherapy, with each cycle of chemo and with each surveillance visit) (**Figure 2 and Table 1**). The primary and secondary endpoints are listed in **Table 2**.

Figure 1. Signatera Molecular Protocol

Sequence tumor tissue to identify unique signature of tumor mutations



Custom design and manufacture personalized mPCR assay for each patient, targeting the top 16 clonal mutations found in tumor



Use personalized assay to test patient's blood for presence of circulating tumor DNA (ctDNA)

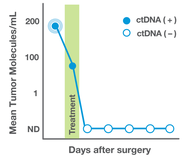


Figure 2. Study Design

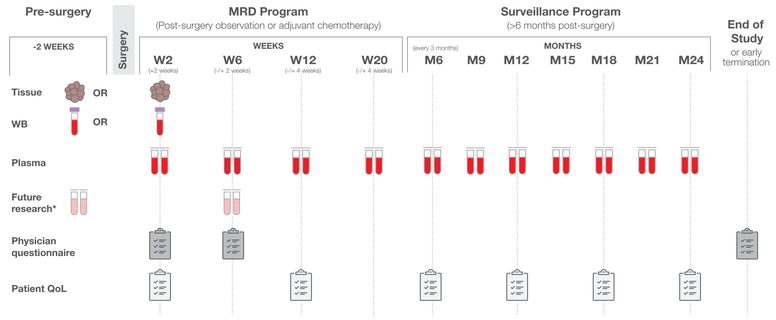


Table 1. Schedule of Events

	Enrollment		MRD Program (Post-Surgery Observation or Adjuvant chemotherapy)			Surveillance (~month 6 onwards)	End of Study or Early Termination
	Pre-surgery -14 days	Week 2 +/- 14 days	Week 6 +/- 14 days	Week 12 +/- 28 days	Week 20 +/- 28 days	Every 3 months through year 2 +/- 45 days	
Informed Consent	X	X					
Confirmation of Inclusion/Exclusion Criteria and Enrollment	X	X					
Demographics		X					
Medical History		X					
Height		X					
Weight		X	X	X	X	X	
ECOG Performance Status		X					
Blood Collection (EDTA)	X						
Blood Collection (Streck)		X	X	X	X	X	
Future research Blood Collection (Streck)	X		X				
FFPE Collection	X						
Laboratory Results	X	X	X	X	X	X	X
Radiology Results		X	X	X	X	X	X
Pathology Results		X					
Physician Questionnaire		X		X			X
Chemotherapy					X		
Adverse Event Reporting		X	X	X	X	X	X
Patient-Reported Outcomes		X		X		X^ (Month 6, 12, 18, 24)	

Legend: *Patients receiving ACT only; ^ every other appointment. Grey box indicates measurement taken only once during the shaded (grey) time period.

Table 2. Study Endpoints

Primary Endpoints	Secondary Endpoints
• To examine the impact of bespoke ctDNA testing on ACT treatment decisions (i.e., the percent of patients who have their ACT regimen increase or decrease at the first time point post-surgery • To determine the percent of patients who recur (ctDNA-positive at any time point, during surveillance) while asymptomatic	• Overall survival • Rate of MRD clearance (MRD+ to MRD-) • Adjuvant treatment rates • Surgery and/or locoregional treatment rates for oligometastatic recurrence • Patient satisfaction • Physician utility

Key Eligibility Criteria

- Patients must have surgically resected stage II/III CRC and FFPE tissue available for analysis
- Patients must be clinically eligible for chemotherapy, tolerant of blood draw up to 20 mL
- Control arm patients must have two years of follow-up data
- Patients must be 18 years of age or older
- Patients must have an ECOG status of ≤2
- Written informed consent must be provided

Study Applications

- Personalized ctDNA testing can guide ACT treatment decisions and serve as a new surrogate endpoint for treatment efficacy and disease status in Stage II/III CRC
- Use of ctDNA to better stratify stage II/III CRC patients into high and low risk groups may detect recurrent CRC early and impact patient survival outcomes
- ctDNA testing can be incorporated into future clinical trials across cancers to assess MRD clearance and monitor recurrence

Impact

- This will be the first real-world study of MRD testing and will provide one of the largest prospective datasets, with serial blood collection at landmark visits, in patients with stage II/III CRC
- **ClinicalTrials.gov Identifier: NCT04264702.**

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