Request for Application for provision of integral biomarkers for patients with resected stage III colon cancer

Summary: NRG Oncology (an NCI National Clinical Trials Network ("NCTN") Group) is seeking a biomarker assay partner to collaborate in a potentially practice-changing, randomized clinical trial (NRG-CR1902). This study will demonstrate the feasibility and clinical benefit of detecting circulating tumor DNA (ctDNA) as a guide to adjuvant chemotherapy decision making following resection of stage III colon cancer.

Rationale: Over 95,520 new cases of colon cancer will be diagnosed in the United States in 2019 of which approximately 35% (33,432) will be stage III. Current guidelines recommend adjuvant therapy in all these patients after surgical resection to reduce the risk of recurrence. However, it is apparent from historical data that a significant proportion will never develop recurrence even without adjuvant therapy and that current standard of care adjuvant therapy (fluoropyrimidine [FP], 5-FU or capecitabine with or without oxaliplatin) only provides incremental benefit in improving disease free survival. Attempts at risk stratification utilizing biomarkers beyond conventional clinicopathologic features such as gene signature testing have not proven reliable in guiding oncologists to consistently identify patients who would benefit from adjuvant chemotherapy. Clearly, more objective biomarkers are needed to inform the treating physician and the patient towards the most appropriate use of adjuvant chemotherapy and also to aid in efficient drug development in this setting.

Multiple recent studies have convincingly shown that the presence of ctDNA from patient plasma following resection to be sensitive prognostic biomarker for recurrence with very high specificity, PPV and NPV, much stronger than traditionally used clinicopathologic features, even tumor stage. This trend was observed even in patients with resected colon cancer demonstrating either “clinically low-risk” or “clinically high-risk” features. These findings generate optimism in introducing ctDNA as a more objective/standardized predictive biomarker for identifying patients with resected stage III colon cancer who may benefit from potentially more or less adjuvant chemotherapy.

Trial Proposal: A North American trial is currently in development through NRG Oncology to test the hypothesis that post-operative ctDNA is a reliable marker of minimal residual disease (MRD) towards stratifying recurrence risk in patients with stage III colon cancer and tailoring intensity of adjuvant chemotherapy accordingly. The study population will include patients with resected stage III colon cancer. For the patients enrolled on this randomized study, all will have plasma analyzed at the time of enrollment. Patients who are ctDNA negative at enrollment will be randomized to an adjuvant dose de-escalation strategy while those who are ctDNA positive at enrollment, or turned ctDNA positive during surveillance, will be randomized to a dose escalation strategy. All patients will also have ctDNA status evaluated at end of completion of planned adjuvant therapy.

Request: We seek proposals for CLIA-certified assays to detect ctDNA from plasma samples of patients enrolled on this study. Academic or commercial clinical labs are eligible. Two strategies for identifying mutations are acceptable: testing resected tumor for mutations with a directed assay for a detected gene in postoperative ctDNA accordingly, or utilization of a broad-panel approach which includes the most common genes found in colorectal cancer. Blood volumes of up to 40 mL can be collected at each time point in the trial. A sensitivity to detect mutations of at least 0.1% allele frequency is needed in order to provide optimal assay performance.

Resources provided by cooperative group mechanism:

The trial will be funded under the NCTN grant which provides funding for protocol development, regulatory functions (excluding IDEs), data management and statistical analysis as well as trial education for the sites. In addition, support is provided to the sites to support the efforts of the sites to enroll patients on to the study. A funding mechanism (BIQSFP) has been identified to provide supplemental funding to support some of the translational and laboratory-based research expenses (it does not support the cost of the assay testing) and will be submitted jointly with the study principal investigators. More details of this mechanism are available at https://www.cancer.gov/about-nci/organization/ccpt/funding/biqsfp. Given the integral nature of this biomarker request, historic funding rates for this mechanism exceed 80%. The applicant should be prepared to provide for this trial material and technological support for assay performance, IDE filings, if applicable, in addition to supplemental funding that neither the NCTN grant nor BIQSFP provides.

Application process:

Proposal details: Proposals should include details of the assay necessary for determining performance in this patient population. Proposals will be kept in confidence, and available for review by the study PIs, NRG leadership, and the peer-review committee. If necessary, CDAs can be established to support additional information. At a minimum, please include the following information on the proposed assay:

1. Assay requirements
   a. Description of the technology utilized for the assay
   b. Optimal plasma volume for the assay
c. Preferred collection tubes, including stability (time from draw to ctDNA extraction)
d. Preferred plasma isolation methodology. Note that participating sites have the ability to process blood to plasma on site, if required.
e. For assays requiring tissue testing, the number of 10um FFPE slides from the surgical specimen needed for the sequencing assay. Please note that fresh tissue will not be available.

2. Assay performance
a. Sensitivity of the ctDNA assay at optimal plasma volume, and impact on sensitivity for lower plasma volumes. Please report as both absolute mutant alleles per mL and % mutant allele frequency in a background of wild type. We anticipate that at least 0.1% allele frequency is needed to provide optimal assay performance.
b. Percent of colorectal cancer patients that may have theoretically detectable mutations using the proposed ctDNA assay. For example whole exon sequencing of APC, TP53, KRAS, NRAS, and BRAF would provide detectable mutations for 90% of the CRC population based on published mutation distributions.
c. Specificity of the assay, with and without prior knowledge of the tissue mutation profile.

3. Laboratory
a. CLIA-compliant laboratory to be utilized. If academic or independent lab is utilized, a letter of support should accompany the proposal.
b. Turn-around time for the assay, from date of receipt of preferred blood component in the central lab.
c. Ability to receive samples on Saturdays.

4. Prior relevant experience
a. Performance of the assay in similar minimal-residual disease clinical situations, if available.
b. In the absence of established performance in a similar cohort, analysis of the test set of 50 patient plasma samples is encouraged. Please note that no funding is available for support of generation of this preliminary clinical data, although the results will be submitted for joint publication.
c. List of prior publications and abstracts. If abstracts are cited, please provide copies of relevant posters or presentations for review.

5. Any additional regulatory and financial resources anticipated

Proposals should be sent no later than 11/1/2019 via email to Chet Cornman (chet.cornman@nsabp.org). Proposals will undergo peer-review by a committee of NRG members and selected outside experts from academia. NCI conflict of interest rules will apply. Questions can be directed to the study PIs, Dr. Arvind Dasari (adasari@mdanderson.org) and Dr. Christopher Lieu (CHRISTOPHER.LIEU@CUANSCHUTZ.EDU) or to the NRG Colorectal Committee leadership (Dr. Thomas George; Chair thom.george@medicine.ufl.edu and Dr. Scott Kopetz; vice-Chair skopetz@mdAnderson.org).