Feasibility Study of Genomic Biomarker Profiling for Patients with Metastatic Colorectal Cancer

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**Abstract**

**Background:** The adoption of Next-Generation Sequencing (NGS) platforms and development of targeted oncology drugs have enabled matching of patients and drugs. The authors undertook an observational, clinical study to explore the feasibility and potential clinical benefits of an upfront approach to the genomic profiling of tumors from metastatic colorectal cancer (mCRC) patients. The study sought to determine the number of drug targetable genomic changes, which occur within mCRC patients including a comparison of patients who progress early versus late.

**Methods:** The study targeted enrollment of 50 mCRC patients within the U.S. Oncology Research Network (USOR) following collection of archival formalin-fixed paraffin embedded (FFPE) samples and genomic testing. Sample collection and processing was performed at Quintiles Central Laboratories followed by testing and bioinformatic analysis at the Quintiles EA Genomic Laboratory. Genomic profiling was performed on the Ion Torrent PGM following enrollment of tumor DNA via the AmpliSeq Cancer Hotspot Panel v2 assay, enriching for hotspots within 50 cancer-related genes. Clinical annotation and reporting to the doctors was provided by N-of-One. Basic demographic and clinical information was collected but formal disease monitoring and follow-up was not performed. Clinicians were asked to report the impact of the genomic test report on patient recommendations.

**Results:** The study enrolled and profiled 51 stage IV mCRC patients from July 2013 to October 2013 from 14 sites in the U.S.; one additional patient was enrolled over the targeted number. Subjects were stratified by time to progression prior to entering the study. The study population was evenly distributed across early (≤1 year) and late (≥1 year) progression. Overall, 100 mutations were identified, including 84.3% of patients had variant associated with approved therapies in other indications, and 80% of patients had variant associated with open clinical trials. Of these 43 patients, 32 had multiple biomarkers with associated therapies. Overall, more than 100 mutations were identified including alterations in KRAS, BRAF, EGFR, PIK3CA, GNAS, TP53, APC, and other genes. The number of actionable mutations was not associated with progression status. Drugs recommended clinical trials following profiling and reporting of genomic alterations in 15 out of the 43 patients (35%) that had actionable mutations.

**Conclusions:** The outcome of this observational study demonstrates the feasibility of rapid screening and reporting of NGS genomic results targeting actionable mutations in mCRC. The lack of an association between early and late progressors, suggests that a greater sample size will be required for future studies. The reported impact on clinician recommendations indicates the value of the results to inform treatment and clinical trial decisions.

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**Background**

**Introduction**

- Cancer genomics is moving into practice driven by the increased molecular complexity of cancer and drugs that target those genomic alterations.
- Exploration of targeted agents in cancer; 22% of the pipeline agents currently in pivotal trials are being developed in a biomarker-defined patient population.
- Recent technical development of genomic platforms enables rapid and broad genomic profiling.
- Patient pro-profiling platform:

  - The Challenge: efficient execution of programs targeting niche oncology populations with specific genomic alterations.
  - How do I cost-effectively develop a drug with an anticipated high screen failure rate in a timely fashion?

**Potential solution**

- Remove barriers to patient participation in clinical trials: multiple testing allows for efficient use of scarce tumor samples and rapid testing of the sample ensures patients are not delayed in receiving treatment.
- Genomic profile patients to match study criteria prior to site startup.
- Clinically annotate and report results to clinician.

**Feasibility study to demonstrate pre-profiling operational platform**

**Summary:**

- mCRC 50 patient trial with 50 gene NGS profiling and reporting to clinicians performed collaboration with U.S. Oncology Research (USOR) Network.
- Potential of rapid execution of proof of concept studies.
- N-of-One. Basic demographic and clinical information was collected but formal disease monitoring and follow-up was not performed. Clinicians were asked to report the impact of the genomic test report on patient recommendations.

**N-of-One.**

- The outcome of this observational study demonstrates the feasibility of rapid screening and reporting of NGS genomic results targeting actionable mutations in mCRC. The lack of an association between early and late progressors, suggests that a greater sample size will be required for future studies. The reported impact on clinician recommendations indicates the value of the results to inform treatment and clinical trial decisions.

**Operational results**

**Pilot study description**

**Ion Torrent PGM NGS Platform**

**Genomic test turn-around-time (TAT) summary**

**Genomic & clinical results**

**Results of Genomic Analysis & Clinical Annotation**

(3 categories of actionable genomic alterations)

**Distribution of mutations in patient population**

**Genomic variants associated with approved therapies in mCRC**

**Influence of genomic data on clinician decision making**

**Discussion**

- Patient pre-profiling may rapidly identify qualified patients for biomarker-driven oncology drug development.
- Pre-profiling may improve trial timelines by increasing the pool of potential candidates participating in clinical trials.
- Implementation of pre-profiling will require collaboration across key stakeholders including sponsors, CROs, clinicians and patients.