Background

Adjuvant chemotherapy has reduced the risk of tumor recurrence and improved survival in patients with resected colorectal cancer (CRC).

Early clinical utility of circulating tumor DNA (ctDNA) pre- and post-surgery has been reported across various types of solid tumors, including CRC. The analysis of ctDNA status can be utilized as a non-invasive biomarker for risk stratification and to monitor the effectiveness of adjuvant chemotherapy.

The study utilizes a personalized, tumor-specific ctDNA analysis in whole-exome sequencing of tumor tissue samples and post-surgery samples to establish the registry data in stage II-IV CRC patients who underwent surgical resection as part of CIRCULATE-Japan project (Fig. 1).

Study design

The study utilizes a personalized, tumor-informed ctDNA assay (Signature™ bespoke multiplex-PCR NGS assay) based on whole-exome sequencing of tumor tissue samples.

The procedure of ctDNA assay is outlined in "Schematic of Molecular Protocol (Fig. 3)."

Blood samples will be collected at following time points; at pre-surgery and 1, 3, 6, 12, 18, 24, 30, 36 and 48 months post-surgery, and at the same time the CT image will be performed.

Mutations in RAS, BRAF, and microsatellite instability tests validated by PCR methods will be assessed centrally.

Key eligibility criteria:

Histologically confirmed colorectal adenocarcinoma

The primary location of the tumor is the colon or rectum (excluding appendix, and anal canal cancer).

Histologically confirmed colorectal adenocarcinoma

Age ≥ 20 years

ECOG PS 0-1

Written informed consent

Primary endpoint:

Disease-free survival

Secondary endpoint:

Overall survival

dctDNA status at each time point

Association between clinicopathological characteristic and gene alterations

Comparison of time to relapse by ctDNA

and computed tomography (CT)

CIRCULATE-Japan project overview

The VEGA trial: A randomized trial to evaluate the non-inferiority of observation vs. adjuvant CAPOX in GALAXY participants who are high-risk stage II or low-risk stage III with absence of ctDNA at 1-month post-surgery.

The ALTARA trial: A randomized trial to evaluate the superiority of FTD/TPI over placebo in GALAXY participants with ctDNA that remains positive after the standard adjuvant therapy.

Translational Research

Planned analysis #1: Association between CMS phenotype and RNA-seq data

RNA-seq

CMS 1: MSI-immune

CMS 2: cancer-related

CMS 3: metabolic

CMS 4: research/pro

We analyze specific molecular signatures and pathways in ctDNA positive and early relapse cases.

Planned analysis #2: Analysis of resistance in adjuvant chemotherapy

Estimating information of treatment and oncogenic factor

Identification of biomarker at recurrence by comparing whole-exome sequencing of surgical and recurrent specimen

Analysis of the association between tumor heterogeneity and treatment sensitivity/resistance

Estimating the molecules responsible for the acquisition of treatment resistance

Verification of treatment resistance factors using cell lines and PDX established from specimens

Identification of novel therapeutic targets

References


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Figure 3. Schematic of Molecular Protocol

Figure 2. GALAXY study schema

Figure 1. CIRCULATE-Japan study schema