# Prospective Observational Study Monitoring Circulating Tumor DNA in Resectable Colorectal Cancer Patients Undergoing Radical Surgery: GALAXY Study in CIRCULATE-Japan (trial in progress)

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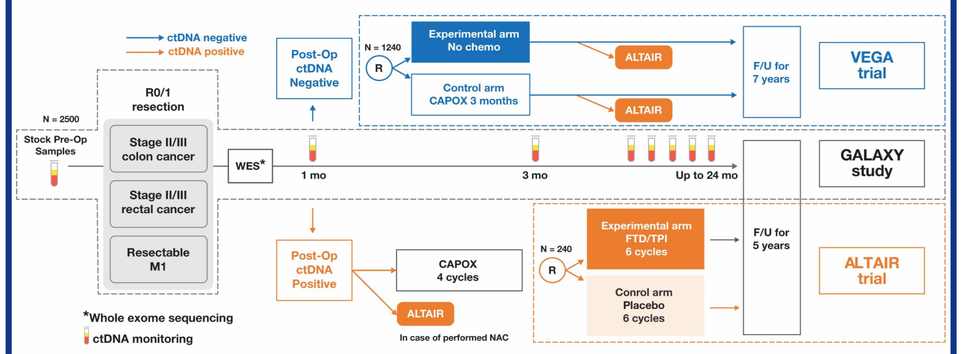
## Background

- 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[1,2,3].
- Analysis of ctDNA status can be utilized as a non-invasive biomarker for risk stratification and to monitor the effectiveness of adjuvant chemotherapy.
- We are conducting a prospective, observational study to monitor the ctDNA status and to establish the registry data in stage II-IV CRC patients who underwent surgical resection as part of CIRCULATE-Japan project (Fig. 1).

## CIRCULATE-Japan project overview

### Figure 1. CIRCULATE-Japan study schema

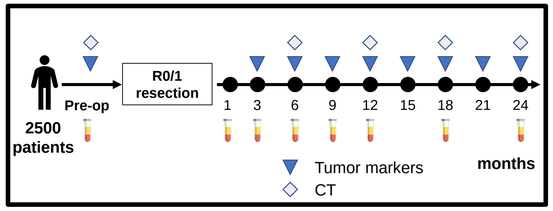



**The VEGA trial:**
**A randomized trial to evaluate the non-inferiority of observation vs. adjuvant CAPOX in GALAXY participants who are high-risk stage II or low-risk stage III with absence of ctDNA at 1-month post-surgery.**

**The ALTAIR 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.**

## Study design

### Figure 2. GALAXY study schema




**Primary endpoint:**
- Disease-free survival

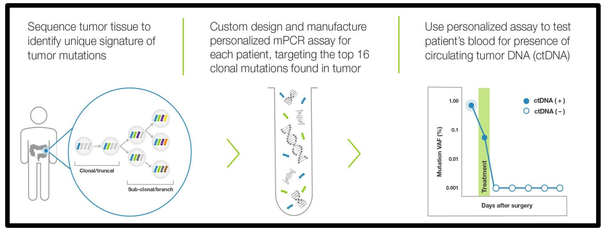
**Secondary endpoint:**
- Overall survival
- ctDNA status at each time point
- Association between clinical characteristic and gene alterations
- Comparison of time to relapse by ctDNA and computed tomography (CT)

- The study utilizes a personalized, tumor-informed ctDNA assay (Signatera™ bespoke multiplex-PCR NGS assay) based on whole-exome sequencing of tumor tissue sample.
- 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, 9, 12, 18, and 24 months of post-surgery, and at the same time the CT image will be performed.
- Mutations in *RAS*, *BRAF* and microsatellite instability tests by validated 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).
- Curative resection is planned for stage II or III in UICC 8th edition, or R0 resection is planned for relapse or stage IV colorectal cancer.
- Age ≥ 20 years
- ECOG PS 0-1
- Written informed consent

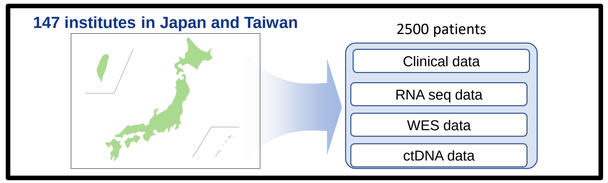
### Figure 3. Schematic of Molecular Protocol



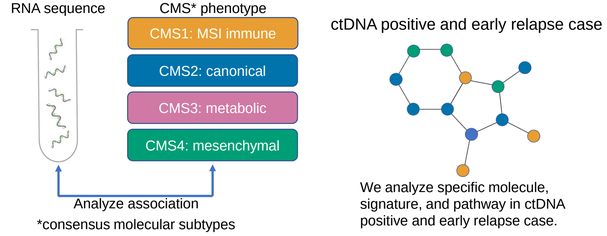

- WES analysis of tumor tissue and blood samples will be performed for each patient to select the patient-specific and clonal 16 single nucleotide variants (SNV).
- Patient-specific multiplex-PCR assays targeting 16 somatic SNV and NGS will be used to detect patient-specific tumor DNA in blood collected pre- and post-surgery.

## Translational Research

### Database about CRC patients

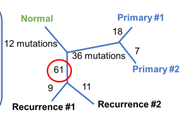



### Planned analysis #1: Association between CMS phenotype and RNA-seq data



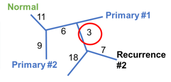

### Planned analysis #2: Analysis of resistance in adjuvant chemotherapy

Extracting information of treatment and oncogenic factor
- Identification of dominant clone at recurrence by comparing exome sequencing of surgical and recurrent specimens
- 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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2. Coombes RC, et al. Clin Cancer Res 2019;25:4255–63.
3. Reinert T, et al. JAMA Oncol 2019 May 9;5:1124-1131.

## Acknowledgment

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