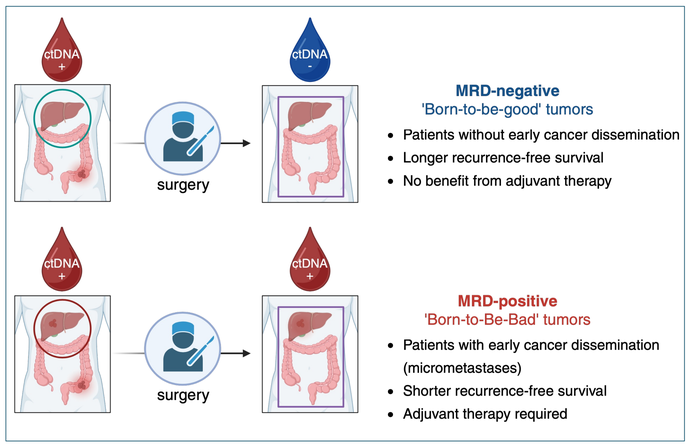
# A precision medicine trial leveraging tissue and blood-based tumor genomics to optimize treatment in resected stage III and high-risk stage II colon cancer patients: The SAGITTARIUS trial

SAGITTARIUS

Funded by the European Union

## Background

- Post-surgical circulating tumor DNA (ctDNA) testing can detect molecular residual disease (MRD) [1,2].
- Post-surgical and post-adjuvant chemotherapy (ACT) ctDNA detection is associated with worse recurrence-free survival (RFS) in stage I-III colorectal cancer (CRC) patients. [2-6]
- ctDNA is a prognostic biomarker with predictive potential of ACT efficacy and disease recurrence in CRC. [4-7]
- Prospective studies and trials assess ctDNA for guiding treatment decisions in stage II-III colon cancer patients [8-11].
- Ongoing randomized clinical trials are adjusting ACT intensity based on MRD status [12,13].
- Unfortunately, intensified ACT is curative in only a proportion of MRD-positive cases [9].
- New personalized treatment strategies are needed to increase adjuvant efficacy in molecularly defined colon cancer patient subgroups.




Post-surgery liquid biopsy detects Minimal Residual Disease (MRD) in colon cancer patients, distinguishing two tumors subtypes with different clinical features.

## Study Design

SAGITTARIUS is a Phase III randomized clinical trial (RCT) aiming at proving the efficacy of using ctDNA detection to guide the adjuvant clinical management in resected stage III and high-risk stage II colon cancer patients, using a tissue-based personalized treatment approach.

Patients are stratified based on post-surgery ctDNA status and molecular biomarkers identified in tumor tissue specimens and then randomized accordingly in two embedded RCTs: Trial-1 for ctDNA-positive patients, and Trial-2 for ctDNA-negative patients.

## Methods

MRD status is determined using the tumor-informed, personalized ctDNA test (Signatera™, Natera, Inc.).

Tumor tissue comprehensive genomic profiling (TruSight™ Oncology Comprehensive EU, Illumina, Inc.) is used to determine molecular biomarkers as microsatellite status (MSI), tumor mutational burden (TMB), gene mutations (mut) and amplification (amp).

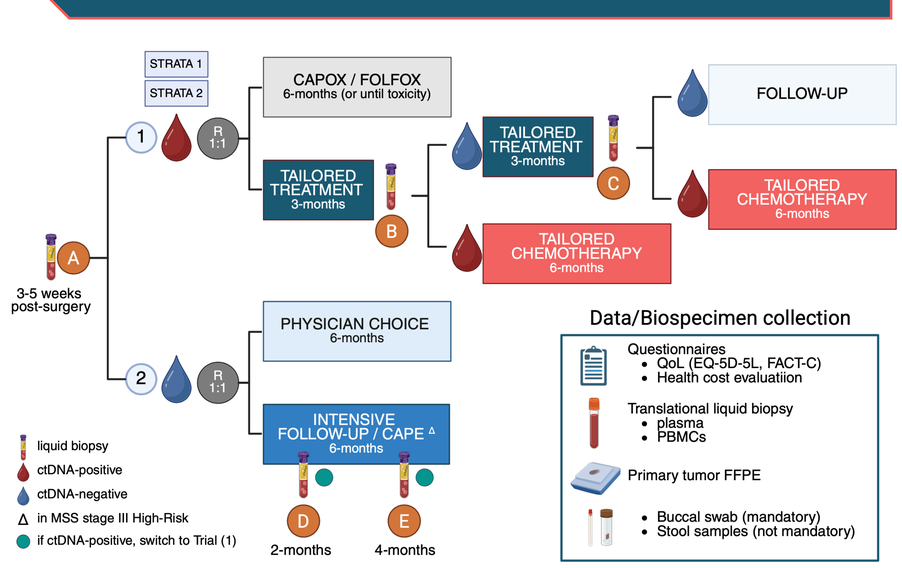
Tumor imaging assessment (CT-scan) is performed before randomization and subsequently: every 3 (Trial-1) or 6 (Trial-2) months for 2 years, then every 6 (Trial-1) or 12 (Trial-2) months for 3 years.

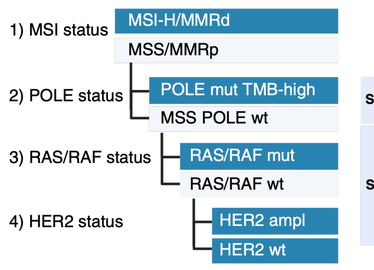
Quality of life questionnaires (FACT-C and EQ-5D-5L) and health costs data are longitudinally collected for Quality of Life and Cost Effectiveness analyses.

Biospecimens, including archival tumor tissue, serial blood samples, buccal swabs and stool specimens, are collected for exploratory analyses.

### KEY FEATURES

1. *Diagnosing **molecular residual disease** after surgery with curative intent*
2. *Establishing the efficacy of a **ctDNA-based tailored** adjuvant strategy compared to **one-size-fits-all** conventional adjuvant chemotherapy in molecularly defined colon cancer patients*
   - *Curbing the risk of relapse and improving survival in ctDNA-positive patients*
   - *Reducing toxicity and improving quality of life in ctDNA-negative patients*

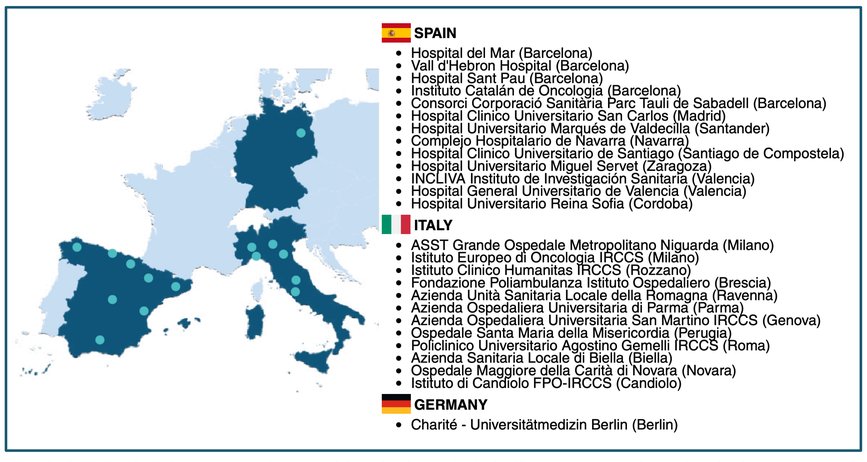



| | MOLECULAR BIOMARKERS | TAILORED | |
|---|---|---|---|
| | | TREATMENT | CHEMOTHERAPY |
| STRATA 1 | MSS RAS/RAF mut | CAPOX | A) TEMIRI B) FOLFIRI |
| STRATA 2 | MSI-H | nivolumab+ipilimumab | CAPOX |
| | MSS POLE mut | nivolumab+ipilimumab | CAPOX |
| | MSS HER2 ampl | trastuzumab+pertuzumab | CAPOX |
| | MSS Multiple WT | FOLFOX+panitumumab | FOLFIRI |

The SAGITTARIUS trial design schema (upper panel), and the molecular biomarker-based stratification factors with hierarchical biomarker priorities consort (lower panel, left) and tailored treatment and chemotherapy associated per each tumor genetic subtype (lowe panel, right).

## Study Sites




The SAGITTARIUS clinical networks includes 26 Institutions within 3 different Eurpean Countries (Spain, Italy and Germany)

## Endpoints

| | |
|---|---|
| Primary | • 2-year RFS in ctDNA-positive patients |
| Secondary | • 2-year RFS in ctDNA-negative patients<br>• 3- and 5-years OS<br>• Safety and tolerability<br>• Seroconversion (ctDNA clerarance) rate<br>• Assesment of FACT-C and EQ-5D-5L |
| Exploratory | • New biomarkers in ctDNA+ vs ctDNA- |

## Sample size

| | |
|---|---|
| Assumptions | • Combined HR=0.63 in overall Trial-1<br>❖ Expected HR=0.80 in Strata-1<br>❖ Expected HR=0.50 in Strata-2<br>• 80% power; 2-sided alpha=0.05 |
| Sample size | • 156 events are required<br>➢ 200 ctDNA-positive patients randomized in Trial-1 |

## Key Eligibility Criteria

| | |
|---|---|
| Main Inclusion criteria | • Histologically confirmed diagnosis of stage III or high-risk stage II colon cancer<br>• Availability of primary tumor FFPE block<br>• ECOG performance status 0-1<br>• Normal organ functions |
| Main Exclusion criteria | • History of another neoplastic disease (unless in remission > 5 years)<br>• Evidence of metastatic disease<br>• Macroscopic or microscopic evidence of residual tumor (R1 or R2 resection)<br>• Acute or subacute intestinal occlusion<br>• Clinically relevant cardiovascular disease<br>• Known history of HIV, Hepatitis B/C, TB<br>• Pre-existing neuropathy > grade 1 |

## Other Embedded Analysis

| | |
|---|---|
| Health Economics | Evaluating the cost-effectiveness of SAGITTARIUS approach |
| Quality of Life | Assessing the impact on health-related quality of life for people with colon cancer |
| OMICs | Understanding the biological process behind disease relapse |

## References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Trial SAGITTARIUS

sagittarius-eu

www.sagittarius-horizon.eu

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***Clinicaltrial.gov:*** ***NCT06490536***

***Sponsor:*** ***IFOM ETS - The AIRC Institute of Molecular Oncology, Milano, Italy***
*sagittarius@ifom.eu*

***Clinical PI:*** ***Clara Montagut, MD PhD, Hospital del Mar, Barcelona, Spain***
*cmontagut@psmar.cat*



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