TPS3647 Poster Session

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 (CC) patients (pts): The SAGITTARIUS trial.

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Background: Circulating tumor DNA (ctDNA) testing has emerged as a transformative tool for detecting molecular residual disease (MRD). Multiple prospective trials have demonstrated the potential of ctDNA in guiding treatment decisions for stage II-III CC pts. Numerous ongoing randomized clinical trials (RCTs) are adjusting adjuvant chemotherapy (ACT) intensity based on MRD status. However, data from ctDNA-guided trials, including PEGASUS (NCT04259944), reveal that intensified ACT is curative in only a small proportion of MRD cases. To address this limitation, the SAGITTARIUS RCT was designed to evaluate whether combining ctDNA detection with targeted agents selected on the basis of tissue-based comprehensive genomic profiling (CGP) can optimize treatment in high risk (i.e. MRD+) pts while sparing low risk (i.e. MRD−) from unnecessary toxicity. **Methods:** SAGITTARIUS is a Phase III RCT evaluating ctDNA and tissue-guided personalized post-surgical management in resected stage III and high-risk stage II CC pts. Tumor-informed, personalized ctDNA test (Signatera, Natera, Inc.) and CGP (TruSight™ Oncology Comprehensive EU, Illumina, Inc.) are used to determine MRD status and tumor genomic landscape, respectively, including genetic mutation (mut) and amplification (ampl), tumor mutational burden (TMB) and microsatellite instability (MSI) status. Pts are stratified based on post-surgery (3-5 weeks) ctDNA status into two embedded RCTs:Trial-1) ctDNA-positive (ctDNA+) ptsare further stratified based on MSI and RAS/RAF status and randomized 1:1 to standard 6-month ACT (CAPOX/FOLFOX) or personalized treatment (PT) guided by CGP biomarkers with reassessment of ctDNA status to guiding subsequent therapies (chemotherapy regimens in ctDNA+ or maintenance and follow-up in seroconverted; Trial-2) ctDNA-negative (ctDNA−) ptsare randomized 1:1 to a physician-choice strategy or observation with ctDNA reassessed at 2 and 4 months and, in cases of positivity, cross over to Trial-1. PT include 3-month CAPOX followed by FOLFIRI or TEMIRI based on MGMT status (RAS/RAFmut), Ipilimumab + nivolumab (MSI and TMB-high POLEmut), pertuzumab + trastuzumab (HER2-ampl), FOLFOX + panitumumab (RAS/RAF/HER2 wild-type). The primary endpoint (EP) is 2-year recurrence-free survival (RFS) in ctDNA+ pts. Secondary EPs include 2-year RFS in ctDNA− pts, 3- and 5-year overall survival, and ctDNA conversion rate. Quality of life and health costs data are collected for cost effectiveness analysis. Biospecimens, including archival tumor tissue, serial blood samples, and buccal swabs, are collected for exploratory analyses. To detect a hazard ratio of 0.6325 for ctDNA-guided PT vs standard ACT, 200 ctDNA+ pts will be randomized in Trial-1. Recruitment began in October 2024 across 26 institutions in Italy, Spain, and Germany. Clinical trial information: NCT06490536. Research Sponsor: European Union; 101104657.