O-11 Monitoring molecular residual disease by circulating tumor DNA in resectable colorectal cancer: Molecular subgroup analyses of a prospective observational study GALAXY in CIRCULATE-Japan

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Background: Identifying molecular residual disease (MRD) using circulating tumor DNA (ctDNA) analysis after curative surgery could facilitate the personalization of adjuvant therapies and early intervention in patients with colorectal cancer (CRC). This study conducted adaptive platform trials, namely CIRCULATE-Japan, comprised of a large-scale patient-screening registry to monitor MRD status (GALAXY), followed by two ctDNA-guided phase III trials (VEGA and ALTAIR), which aim to refine adjuvant therapy in patients with resectable CRC.

Methods: The ctDNA status in plasma was investigated periodically at pre- and post-surgery for up to 2 years using SignateraTM, a personalized, tumor-informed ctDNA assay designed to track 16 patient-specific somatic variants based on whole-exome sequencing of the tumor tissue and matched normal blood. Median ctDNA levels were measured in mean tumor molecules (MTM) per milliliter (mL) of plasma. RAS and BRAF V600E mutations and MMR status in tumor tissue were assessed using polymerase chain reaction-based methods. Moreover, the association of ctDNA status with tumor biomarkers status were also investigated.

Results: The GALAXY study enrolled 1,236 patients as of 28 February 2021. Of the patients, 1058 patients had their presurgery ctDNA status. In this analysis, 400 patients who had their pathological, and tumor biomarker statuses were evaluated. RAS, BRAF V600E mutations (MT), and MSI-high (MSI-H) status were identified in 169 (42%), 24 (6%), and 30 (8%) patients, respectively. Patient-specific SignateraTM assays targeting 16 variants were designed for 100% of the patients. Moreover, baseline ctDNA at presurgery was detected in 92% (367/400) of the patients with 80% (28/35),

96% (129/135), and 94% (143/152) in pathological stage (pStage) I, pStage II, and pStage III, respectively. Furthermore, positive ctDNA status at presurgery was significantly associated with advanced pStage ($p = 0.004$), pT ($p < 0.001$), and lymphovascular invasion ($p = 0.043$), but not associated with RAS/BRAF and MMR statuses. The median ctDNA levels at presurgery were observed to be higher in patients with advanced stages (pStage I, 0.73; pStage II, 3.66; and pStage III, 4.54 MTM/mL; $p < 0.001$). Patients with BRAF V600E mutant tumors had a higher presurgical median ctDNA level compared with RAS MT or wild-type (WT) RAS/BRAF in pStage II (RAS/BRAF WT, 3.69; RAS MT, 1.35; and BRAF MT, 11.65 MTM/mL; $p = 0.069$) and pStage III (RAS/BRAF WT, 3.91; RAS MT, 2.73; and BRAF MT, 9.50 MTM/mL; $p = 0.136$). Consequently, positive ctDNA status 4 weeks after post surgery was similar regardless of RAS and BRAF mutational status (RAS/BRAF WT, 15%; RAS MT, 18%; and BRAF MT, 13%; $p = 0.80$), while MSI-H patients tended to have a lower positive ctDNA status 4 weeks after post surgery (MSS, 17%; MSI-H, 7%; $p = 0.198$) although the difference was not significant.

Conclusions: Preoperative ctDNA was detected in greater than 90% of the patients by personalized ctDNA assay based on unique somatic variants specific to each patient. The associations of ctDNA-based MRD status and tissue biomarkers were observed, suggesting the ctDNA potential for reflecting biological aggressiveness related to biomarkers. However, further investigations are needed.

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