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REVIEW

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Current Advancements and Novel Treatment Strategies for Colorectal Cancer

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ABSTRACT Colorectal cancer (CRC) is a serious health problem around the world. It is the third most common cancer and the second leading cause of cancer-related deaths. The primary treatment for non-metastatic CRC is surgery and/or chemoradiotherapy along with surgery, while standard treatments for unresectable CRC include the combination of chemotherapy, biological agents (monoclonal antibodies), targeted therapy, and immunotherapy. However, standard care cannot satisfactorily reduce recurrence and mortality rates. Therefore, more effective strategies need to be developed for managing treatment-resistant tumors. Many researchers have evaluated neoadjuvant chemotherapy for CRC with limited metastasis and operable disease for optimal curative resection by downstaging or decreasing the volume of the tumor and reducing the risk of metastasis. Important updates, guiding our practice and providing novel information, were shared at the 2024 American Society of Medical Oncology's Gastrointestinal Cancers Symposium (ASCO GI). Along with the increase in identified current targets and treatments for metastatic disease, the utility and validation of circulating tumor DNA assays, especially for early-stage/limited metastatic operable CRC, and organ-sparing approaches in patients with rectal cancer who respond to total neoadjuvant treatments were examined in detail. In this review, we summarized the developments specifically for CRC.

Keywords: Novel treatment; advancements; colon cancer; rectal cancer

CIRCULATING TUMOR DNA DYNAMICS IN COLORECTAL CANCER: MORE QUESTIONS THAN ANSWERS

GALAXY TRIAL

The updated results of the prospective GALAXY trial, the observational arm of the CIRCULATE-Japan study (UMIN000039205) involving 157 centers, have been reported. More than 30% of patients with resectable colorectal cancer (CRC) relapse despite receiving preventive standard-of-care treatment.[1] Circulating tumor DNA (ctDNA) may aid postoperative risk stratification and adjuvant chemotherapy (CT) treatment decisions. In this study, 2,783 of the 5,781 patients were excluded for various reasons (mostly because they were included in other clinical studies), and the remaining 2,998 patients were included between May 2020 and October 2023. The median follow-up time was 16.14 months (0.23-42.14 months), and the primary endpoint was considered to be the 24-month disease-free survival (DFS) of surgically resected patients with pathological stages 1-4.

In this study, a tumor-informed, personalized assay (Signatera, Natera, United State, Inc.) was conducted to detect ctDNA. Serial measurements were performed 1, 3, 6, 9, 12, 18, and 24 months after surgery. The relationship between relapse and ctDNA was investigated, and 80% of the patients were found to have T3-T4 tumors, while 15% had Stage 4 dis-

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ease. Among them, 11% of patients received neoadjuvant CT, and 89% underwent surgery. Adjuvant CT was not applied to 62% of patients. Microsatellite instability (MSI) was high in 9% of patients, and relapse occurred in 18% of patients during follow-up.

ctDNA positivity in the minimal residual disease (MRD) analysis interval (MRD window), i.e., between week 2 and week 10 after surgery or the start of adjuvant CT, predicted poorer DFS for all stages [HR for ctDNA negative vs. positive: 10.53 (8.74-12.69), p<0.0001, and 24-month DFS was 85.9% (95%, CI 83.9-87.7) vs. 28.9% (95%, CI 23.4-34.8)]. Also for patients at pathological stages 2-3, ctDNA negative vs. positive HR was 12.05 (9.46-15.34; p<0.0001), and 24-month DFS was 89.3% (95% CI 87.2-91.1) vs. 33.5 (95% CI 26.5-40.7). The recurrence rate was 9.4% in ctDNA-negative patients and 58.8% in ctDNA-positive patients.

In this study, 240 of 445 ctDNA-positive patients were administered adjuvant treatment. The importance of converting the ctDNA-negative status (clearance) in these patients was investigated. While there was no clearance in 68 (28.3%) patients, transient clearance was detected in 61 patients (25.41%), and sustained clearance was detected in 84 patients (35%). For patients receiving adjuvant CT, achieving sustained ctDNA clearance was associated with significantly superior DFS compared to transient clearance and no clearance. While the 24-month DFS for ctDNA-positive patients in the MRD window period after adjuvant CT who had sustained ctDNA-negative status was quite favorable at 90.1% (95% CI: 78.6-95.6), this rate was highly unfavorable at 2.3% (95% CI: 0.02-10.3) for patients with transient clearance and 2% (95% CI, 0.02-9.2) for patients without clearance. Moreover, 98% of patients who showed transient ctDNA clearance and developed radiological or clinical recurrence also developed molecular recurrence by 18 months.

A significant difference in DFS was also found between patients who remained ctDNA-negative and those who were ctDNA-positive at any time during the observation period after the MRD window or after adjuvant CT [HR for all stages: 42 (95% CI, 30.88-57.14) p<0.0001 and 24-month DFS 93.9% vs. 6.6%]. The initial MRD interval and the ctDNA status during surveillance were closely associated with DFS.

A decrease in ctDNA concentration (MTM/mL) at six months with adjuvant CT predicted treatment response and was associated with more favorable clinical outcomes (HR: 6.72, 95% CI: 3.84-11.76, p<0.0001) for patients with complete clearance and those with no clearance at six months. Additionally, the HR was 2.41 (95% CI, 1.42-4.09, p=0.001) for those who developed clearance between 50 and 100% and those who developed clearance between 0 and 50% in the period of MRD window to the sixth month (24-month DFS was 51.1% vs. 29).

Similarly, randomized VEGA and ALTAIR studies are ongoing as part of the CIRCULATE JAPAN study, where ctDNA-based adjuvant treatment strategies are under evaluation.

NRG-GI005 (COBRA) TRIAL: PHASE 2 RESULTS

The detection of ctDNA after curative-intent treatment plays a prognostic role for all stages of colon cancer; however, its effectiveness as a predictive biomarker needs to be determined. The results of the Dynamic study, a prospective randomized controlled trial, supported treatment de-escalation in the absence of detectable ctDNA after surgical resection in Stage 2 colon cancer.

The Guardant Lunar is a tumor-uninformed assay that assesses epigenomic methylation signatures and somatic mutations. In a cohort of 103 early-stage CRC patients, Parikh et al. reported sensitivity and specificity of 55.6% and 100% by conducting this assay.[2]

In the NRG-GI005 study, patients with resected Stage 2A colon cancer who were evaluated by the clinician to not require adjuvant therapy and who were considered suitable to be followed up with active surveillance were included. Patients were randomized into two arms. In arm 1, some patients underwent standard active surveillance, while in arm 2, based on the ctDNA test results, patients were either administered adjuvant FOLFOX or CAPOX if the ctDNA status was positive, or they underwent active surveillance if the ctDNA status was negative. Patients were followed up with radiological imaging every six months. The Guardant LUNAR test, vali-

dated clinically and analytically, was used as the ctDNA test.

Patients who were considered for diagnosis with pT3N0 Stage 2a adenocarcinoma had at least 12 or more lymph nodes surgically removed and were evaluated to be included in the study, and they were randomized into two arms within 14-60 days after surgery. The study compared ctDNA clearance rates six months after randomization for ctDNA (+) patients. The ctDNA status was determined for 596 of 635 patients, and ctDNA (+) was detected in 33 patients (5.54%). Among 16 patients, seven patients with baseline ctDNA (+) were in arm 1 (the active follow-up arm), and nine were in arm 2 (the adjuvant treatment arm). The clearance of ctDNA was present in three patients (43%) in arm 1 and one patient (11%) in arm 2. The one-way Fisher's exact test result was above the predicted value of 0.35, and the p-value was 0.98; thus, the null hypothesis could not be rejected. Therefore, the study could not provide strong evidence that the clearance achieved with six months of adjuvant CT for low-risk Stage 2A colon cancer was better than the ctDNA clearance achieved with active surveillance.

No benefit of the treatment strategy was found for this clinically low-risk population based on ctDNA measurement conducted using the Guardant Lunar assay.

AGITG DYNAMIC-RECTAL STUDY

Although the survival benefit of adjuvant CT following neoadjuvant chemoradiotherapy (CRT) and surgery is not clear, it has been widely adopted and used in patients with locally advanced rectal cancer (LARC). Some researchers found that detecting ctDNA after surgery is a strong prognostic marker in local-stage CRC and may be a potential guide in making adjuvant treatment decisions. In a study, a ctDNA-guided approach to the treatment of Stage 2 colon cancer decreased adjuvant CT use without compromising recurrence-free survival.[3]

AGITG DYNAMIC-Rectal was a multicenter, randomized, controlled Phase 2 study. Patients with an accurate diagnosis of LARC (clinical T3-4 and/or N+), who underwent neoadjuvant CRT and total mesorectal excision (TME) and whose performance status was sufficient for adjuvant CT, were included. Patients were randomly placed in a 2:1 ratio in the ctDNA-guided or standard management (clinician choice) group. A personalized, tumor-informed ctDNA analysis was conducted. For the ctDNA-guided group, patients with a positive result (identified four and/or seven weeks after surgery) were administered fluoropyrimidine or oxaliplatin-based CT for four months. For ctDNA-negative patients, if ypN0 or ypN+, CT was not administered at the clinician's discretion. The primary endpoint of the study was determined based on the rate of adjuvant CT use. An important secondary endpoint was considered to be non-inferiority between the approaches in three-year relapse-free survival (RFS).

The target study sample size was 408 for 80% power; however, the results of 230 eligible patients could be analyzed. The proportion of patients with T4 tumors at baseline was 11% and 8%, N2 disease was 25% and 20%, ypT4 after neoadjuvant therapy was 1.3% and 2.7%, ypN+ was 29% and 31%, and pathological complete response (pCR) was 17% and 12%, respectively, for the ctDNA-guided management and standard management groups. Moreover, ctDNA positivity was 28% in the entire group. At a median follow-up of 36 months, three-year recurrence-free survival was 74% and 82%, respectively (HR: 1.38, 95% CI, 0.76-2.50, p=0.28). Due to the insufficient sample size, no strong evidence could be provided regarding whether ctDNA-guided management was better than standard management.

Using the ctDNA-informed adjuvant treatment approach, a significant reduction was recorded in the rates of CT administration after neoadjuvant CRT and surgery (46% vs. 77%, p<0.001). All ctDNA (+) patients received adjuvant CT, whereas 23% of ctDNA (-) patients received CT, and the three-year RFS was 53% and 83% in these patient groups, respectively (HR: 0.29, 95% CI: 0.15-0.55, p<0.001). Therefore, the risk of disease recurrence in ctDNA-negative patients after surgery was significantly lower than that in ctDNA-positive patients.

The dominant metastasis sites were the lungs (83%) for ctDNA-negative patients and the liver (69%) for ctDNA-positive patients.

BESPOKE CRC STUDY

This was a prospective observational study involving 133 centers in the United States and was the first large study to investigate the role of tumor-informed personalized ctDNA testing in the decision for adjuvant CT and early recurrence detection for Stage 2-3 CRC patients.[4] Between July 2020 and August 2022, 1,784 patients were screened. Among them, 623 patients for whom all data were available were included in the MRD cohort and 655 patients were included in the active surveillance cohort. The MRD window was determined as 1-12 weeks after surgery and 1-12 weeks after adjuvant CT. For patients under observation, the surveillance window was >12 weeks after surgery and >2 weeks after adjuvant CT.

During the MRD period, ctDNA positivity was found to be a strong predictor of worse DFS (HR 12.1, 95% CI: 8.0-18.3, p<0.0001), two-year DFS 91.59% vs. 29.86% for MRD negative vs. positive, respectively. MRD (+) was detected in 6.43% of patients with Stage 2 disease (n=280) and 21.87% of patients with Stage 3 disease (n=343). While administering adjuvant CT benefitted MRD (+) patients, it did not benefit MRD (-) patients (in the absence of adjuvant CT for MRD-positive patients, HR=3.06, 95% CI=1.43-6.56, p=0.0025; for MRD-negative patients, HR=1.47, 95% CI=0.78-2.78, p=0.2316).

During the surveillance period, ctDNA-positivity was a predictor of inferior DFS, independently of adjuvant CT (for patients who received adjuvant CT and were observed without adjuvant CT). For ctDNA (-) vs. ctDNA (+) patients in the adjuvant CT arm, HR=59.98, 95% CI=27.3-131.9, p<0.0001, and two-year DFS was 97.58% vs. 22.56%. The median DFS after the end of adjuvant CT was not reached (NR) vs. 9.7 months. For patients in the observation arm, HR=80.10, 95% CI=30.0-207.0, p<0.0001, two-year DFS was 96.60% vs 13.04%, and median DFS after surgery was NR vs 9.44 months.

When assessed according to the DNA clearance pattern, persistent ctDNA clearance was associated with significantly superior DFS compared to transient clearance or no clearance. Additionally, ctDNA test monitoring provided treatment for oligometastatic cancer, such as surgery, radiofrequency ablation, microwave ablation, stereotactic radiotherapy, and CRT, in up to 40% of patients with recurrence.

ORGAN PRESERVING APPROACHES IN RECTAL CANCER

The risk of distant metastasis in patients with a clinical complete response (cCR) in rectal cancer, who were followed up with a watch-and-wait (WW, non-surgical, organ-sparing) approach, was evaluated and reported in two international registry studies.[5,6] One of these databases included was the International Watch and Wait database (IWWD; International WW database), while the other was the VIKINGO consortium. According to this study, which included both databases, the three-year local tumor regrowth rate was approximately 30%. The rate of distant metastasis for patients who achieved a pCR and were followed up with WW varied between 1 and 4%, whereas this rate was 36% for patients who experienced regrowth while being followed up based on the WW approach, and the difference in the rate between the two groups of patients was statistically significant (p<0.001). Among these patients, an HR of 4.8 (95% CI=3.14-7.49, p<0.0001) was reported for patients with local regrowth compared to those without local regrowth.

Local regrowth after achieving a cCR and managed with the WW approach has a higher risk of subsequent distant metastases compared to those with a near-complete response (<10% cancer cells+) at restaging, if managed with TME. Poorer distant metastasis-free survival was expected for local regrowth irrespective of other independent risk factors, such as the ypT or ypN stage.

While designing future studies, the risk of distant metastasis should be considered in case of local regrowth if organ-preserving management with the WW approach is adopted. For patients evaluated using the WW approach, the risk of local regrowth needs to be decreased by adhering to a strict definition of cCR.

EFFECT OF LAPAROSCOPIC-ASSISTED VS. OPEN SURGERY ON SURVIVAL OUTCOME IN LOW RECTAL CANCER

THE LASRE TRIAL

This was a non-inferiority-based randomized controlled study in which 22 centers from China participated and

compared the oncological results of laparoscopic and open surgical approaches in patients with lower rectal cancer. Only those surgeons who had performed more than 100 laparoscopic TMEs were included in the study, including a review of at least two videos.[7]

In total, 1,070 patients with lower rectal cancer (<5 cm from the dentate line), stages 1 and 2/3, without pelvic lateral LN or distant metastases, were randomly placed in a 2:1 ratio in the laparoscopic TME group or open TME group. The primary endpoint of the study was determined as three-year DFS (time to locoregional recurrence/distant recurrence/death after surgery). More than 60% of the 1,039 patients evaluated in the ITT population had clinical Stage 2/3 disease requiring neoadjuvant CRT. In the two groups, sphincter preservation and median hospitalization time significantly favored laparoscopic surgery. When all stages and Stage 1 and Stage 2/3 patients were evaluated individually, it was found that laparoscopic surgery performed by experienced surgeons was non-inferior to open surgery in terms of three-year DFS and three-year OS of lower rectal cancer patients. Regarding recurrence, the HR in favor of open surgery for Stage 2/3 was found to be 2.72 (0.93-7.95), but the results were statistically not significant (p=0.06).

THE ROLE OF PERITONEAL LAVAGE CYTOLOGY IN RESECTED STAGE 2 AND 3 CRC (PEC-CC)

This was a prospective study that assessed the utility of intraoperative lavage cytology in patients undergoing curative resection, with the participation of 20 member centers of the Japanese Society for Cancer of the Colon and Rectum. Between 2013 and 2017, patients diagnosed with Stage 2 or 3 CRC were included in the study, and lavage cytology was evaluated twice during surgery in patients confirmed to have pStage 2-3 CRC (the first evaluation was made immediately after laparotomy and the second was made right after the specimen was sent). The primary endpoint of the study was the effect of lavage cytology on five-year RFS in patients with pStage 2-3 CRC. The secondary endpoint was the effect of cytology on five-year OS and peritoneal recurrence.[8]

Positive cytology was found in 54 of 1,378 patients (3.9%). In the Stage 2 patient group, the five-year RFS rates for positive and negative cytology were 61.1% and 81.6%, respectively (p=0.023), and the five-year OS rates were 67.1% and 91.7%, respectively (p=0.0083). Negative cytology was associated with better five-year RFS and OS for Stage 2 patients, while no significant difference was found for Stage 3 patients. The peritoneal recurrence rates in Stage 2 patients with positive and negative cytology were 11.8% and 1.5% (p=0.032), respectively, and in Stage 3 patients they were 10.5% and 2.5% (p=0.022), respectively.

Peritoneal lavage cytology was beneficial in predicting peritoneal recurrence after surgical treatment of patients with Stage 2 and Stage 3 CRC.

FIRE-3 STUDY: FIRST-LINE SYSTEMIC TREATMENT DECISION FOR RAS WILD-TYPE METASTATIC CRC WITH CLINICAL BIOMARKER COMBINATION (AIO KRK0306)

The FIRE-3 study compared the effects of first-line FOLFIRI (folinic acid, fluorouracil, and irinotecan) plus cetuximab (FOLFIRI/Cet) to those of FOLFIRI plus bevacizumab (FOLFIRI/Bev) on patients with RAS-wt mCRC.[9] In this study, the effect of primary tumor sidedness (PTS) and the reflection of clinical biomarkers, such as age, gender, liver-limited disease (LLD), and basal serum CEA level, individually or in combination, on OS and the selection of biological agents, were evaluated using statistical analysis methods such as Cox regression models, Weibull models, Holm models, and Bonferroni correction. The model that used a combination of primary tumor location (PTS) and LLD best predicted the clinical benefit outcome of both treatment arms (c-index=0.603, p=0.005).

For left-sided tumors, a significant survival benefit of FOLFIRI/Cet was found over FOLFIRI/Bev in patients without LLD compared to those with LLD (HR=0.62, p=0.02).

For right-sided tumors, FOLFIRI/Bev treatment was significantly associated with greater OS over FOLFIRI/Cet in patients without liver-confined disease compared to those with LLD (HR=2.09, p=0.010).

For the disease limited to the liver, a benefit was noted on the FOLFIRI/Cet side for right colon tumors (HR 0.59, p=0.218); however, this benefit was limited and was not statistically significant for the left colon (HR=0.83, p=0.40).

FIRST RESULTS OF THE CHECKMATE 8HW STUDY

The combination of nivolumab with low-dose ipilimumab (NIVO+IPI) as first-line therapy in patients with MSI-H/dMMR mCRC in the Phase 2 CheckMate (CM) 142 study (NCT02060188) showed strong, long-lasting clinical benefits and was well-tolerated.[10] In this single-arm Phase 2 study, a 64% response rate, 75% PFS plateauing at 24 months, and a 15-month survival of 84% were reported with NIVO+IPI. Therefore, the administration of 3 mg/kg nivolumab every two weeks and 1 mg/kg ipilimumab every six weeks until progression or toxicity was also included in the NCNN guidelines as the initial treatment option for this patient group.

In the Phase 3 randomized Keynote 177 study, two-year and five-year PFS with single-agent pembrolizumab was found to be 48% and 34%, respectively. In this study, pembrolizumab treatment showed a significant median overall survival advantage over the CT arm [77.5 months (95% CI: 49.2 to NR) vs. 36.7 months (95% CI: 27.6-65.3) (n=143); HR, 0.73; 95% CI: 0.53-0.99]. Three-year survival was 61.4% and 50.3%, while the most recently reported five-year survival was 54.8% and 44.2%, respectively. The mPFS was 16.5 months and 8.2 months (HR 0.60, 95% CI: 0.45-0.79), three-year PFS was 42.7% and 13.4%, and five-year PFS was 34% and 7.6%, respectively.[11,12] However, the benefits were reduced compared to CT, especially for the RAS mutant patient group.

The Checkmate 8HW study was a Phase 3 study in which patients with MSI-H/dMMR mCRC were randomly placed in three groups: NIVO+IPI, NIVO, and CT as first-line treatment in a ratio of 2:2:1. The single-agent NIVO regimen included the administration of 240 mg of nivolumab every two weeks for the first six doses, followed by the administration of 480 mg of nivolumab every four weeks. The NIVO+IPI combination arm consisted of 240 mg of NIVO+ IPI 1 mg/kg in four doses every three weeks, followed by NIVO 480 mg every four weeks. In the CT cohort, modified FOLFOX6 (fluorouracil, leucovorin, and oxaliplatin) or FOLFIRI (fluorouracil, leucovorin, and irinotecan) was administered based on the investigator's preference, and 75% of these patients also received bevacizumab or cetuximab. The PFS results of NIVO+IPI vs. CT after a median follow-up of 24.3 months were reported in ASCO GI 2024.

Of the 303 patients, 21% had a KRAS/NRAS mutation, and 26% had a BRAF mutation. In the NIVO+IPI combination arm, mPFS was not achieved, while in the CT arm, mPFS was 5.9 months and two-year PFS were 72% and 14%, respectively [HR: 0.21 (95% CI=0.13-0.35) p<0.0001]. For all patient subgroups, including patients with KRAS/NRAS mutations or baseline liver, lung, or peritoneal metastases, NIVO+IPI was superior to CT, providing a 79% risk reduction in disease progression. NIVO+IPI had superior PFS compared to CT, fewer grade 3-4 adverse events, and no new safety issues.

NEST-1 STUDY: EFFECTIVENESS OF NEOADJUVANT BOTENSILIMAB PLUS BALSTILIMAB (BOT/BAL) IN RESECTABLE MMR PROFICIENT AND DEFICIENT CRC

Effective treatment methods need to be developed for the preserved mismatch/microsatellite stable (pMMR/MSS) group, which represents the majority of CRC cases (85-95%).[13]

Botensilimab (BOT-AGEN 1181) is a multifunctional next-generation CTLA-4 inhibitor antibody. Balstilimab (BAL-AGEN2034) is an anti-PD-1 antibody with a response rate of >20% in patients with heavily pretreated pMMR/MSS metastatic CRC.

The NEST-1 study (NCT05571293) is a Phase 2 study in which neoadjuvant BOT and BAL therapeutic interventions were evaluated in CRC patients who are surgical candidates. The patients received BOT 75 mg and BAL 240 mg on day 1 and received BAL 240 mg in week 2. The patients underwent surgery 1-6 weeks after administering the second dose of BAL.

Pathological response (at least 50% tumor reduction) was achieved in six of nine (67%) patients with pMMR/MSS tumors. Major pathological response (at least 90% tumor reduction) was achieved in all three patients (100%) with dMMR/MSI-H tumor. In the MSS population, tumor regression

rates were 100% (complete response-CR) in two patients, 90% in one patient, 85% in one patient, 50% in two patients, 25% in one patient, and 10% in one patient. No response was found in one patient. In the MSI-H population, a tumor reduction rate of 100% (CR) was reported in two patients and 98% in one patient. No surgical delay occurred due to any side effects.

All seven patients with ctDNA (+) at the beginning of the screening process became ctDNA (-), and 11 patients with ctDNA (-) remained negative after surgery. Immunohistochemical/immunofluorescence examination of the tumor after treatment showed significant T cell infiltration, regulatory T cell reduction, and dendritic cell/myeloid repolarization.

To summarize, neoadjuvant dual immunotherapy in the NEST-1 trial revealed a robust response and long-term ctDNA/MRD negativity for MSS and MSI-H resectable CRC.

CODEBREAK 300 STUDY: HEALTH-RELATED QUALITY OF LIFE (QOL) DATA

The CodeBreak 300 study is a Phase 3 study comparing the effectiveness of the combination of the KRAS g12c inhibitor sotorasib and panitumumab to that of standard treatment (trifluridine/tipiracil or regorafenib) with a 51% reduction in the risk of progression in the experimental arm.[14] Patient-reported QoL data were shared in the meeting conducted in 2024.

Quality-of-life data were obtained from the patients through BFI, BPI, EORTC QLQ-c30, and PGI-C questions and were repeated at baseline and every four weeks. Changes from baseline to the end of week 8 were assessed for these scales using a mathematical risk management model. Time to deterioration was evaluated for the worst pain (BPI) and worst fatigue (BFI), and the EORTC QLQ-c30 scales were analyzed based on Kaplan-Meier curves and Cox proportional hazards models.

For the chemorefractory CRC patient group, administering a combination of 960 mg of sotorasib and panitumumab showed superiority to the investigator's choice of standard treatment regarding HRQoL data and efficacy.

SUMMARY OF SOME SELECTED STUDIES

Comparison of Trifluridine/Tipiracil and Bevacizumab Every Two Weeks vs. Trifluridine/Tipiracil Monotherapy in Chemorefractory Metastatic CRC (JCOG2014/ ROBITS) Phase 3 study

In this Japanese Clinical Oncology Group study, the results of 152 patients were reported due to early termination, according to the results of the Sunlight study. The mPFS was 2.4 months for the trifluridine/tipiracil monotherapy arm and four months for the trifluridine/tipiracil with bevacizumab combination therapy arm (HR=0.60, 95% CI=0.43-0.86). The patients in the combination arm had longer PFS and fewer hematologic side effects.

Retrospective Study Investigating the Prognostic Significance of KRAS G12D Mutation for RAS-Mutated CRC

In this retrospective Japanese study, the RAS status was evaluated retrospectively with a PCR (polymerase chain reaction) kit. Among RAS mutations, KRAS G12D constituted 27.9% (80/287) of the total. The PFS and OS results of RAS mutant patients did not differ significantly between the KRAS G12D group and the non-KRAS G12D group. Therefore, the researchers reported that the KRAS G12D mutation does not act as an independent prognostic factor for RAS-mutated CRC.

Fruquintinib and Capecitabine vs. Capecitabine Single-Treatment as Maintenance Therapy in Metastatic CRC

In this Phase 1b/2 study, 110 patients diagnosed with metastatic CRC and whose disease was controlled after at least six cycles of first-line standard CT were randomly placed in two groups in a 1:1 ratio, which included the capecitabine monotherapy (Cap) group and the fruquintinib and capecitabine (Fru+Cap) group. The Cap group had mPFS of 3.8 months (2.3-5.7), while the Fru+Cap group had mPFS of 9.1 months (5.0-NA). The overall response rate (ORR) was 21.4% for the Fru+Cap group, while the ORR was 0% in the Cap group. The most common adverse events reported for patients with grade >3 CRC in the combination treatment group were hy-

pertension (11.1%), voice change (5.6%), oral mucositis (5.6%), and increased bilirubin levels (5.6%).

Clinical Characteristics and Treatment Outcomes in CRC Patients with Somatic BRCA1/2 Mutations

In this single-center study, patients with somatic BRCA 1/2 mutations who underwent next-generation sequencing from blood or tissue were evaluated. The mutation pathogenicity of each mutation was annotated using public genomic databases such as ClinVar.

Somatic BRCA 1/2 mutations frequently co-occur with pathogenic POLE mutations in patients with CRC. However, the therapeutic benefit of platinum-based CT and PARP inhibitors has not been demonstrated.

Investigations on the effects of the presence of BRCA alterations, homologous repair defects, and germline BRCA 1/2 mutations on CRC are ongoing.

CONCLUSION

This study summarized the utility and validation of ctDNA analyses, especially for early-stage/limited metastatic operable CRC, organ-preserving approaches in patients with rectal cancer responding to total neoadjuvant therapies, and next-generation dual immune blockade therapy for patients with resectable CRC and metastatic CRC.

Source of Finance

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Şuayip Yalçın;* ***Design:*** *Şuayip Yalçın;* ***Control/Supervision:*** *Şuayip Yalçın;* ***Data Collection and/or Processing:*** *Şuayip Yalçın, Seda Kahraman;* ***Analysis and/or Interpretation:*** *Şuayip Yalçın, Seda Kahraman;* ***Literature Review:*** *Şuayip Yalçın, Seda Kahraman;* ***Writing the Article:*** *Seda Kahraman;* ***Critical Review:*** *Şuayip Yalçın.*

REFERENCES

1. Kotani D, Oki E, Nakamura Y, et al. Molecular residual disease and efficacy of adjuvant chemotherapy in patients with colorectal cancer. Nat Med. 2023;29(1):127-134. [Crossref] [PubMed] [PMC]
2. Parikh AR, Van Seventer EE, Siravegna G, et al. Minimal residual disease detection using a plasma-only circulating tumor dna assay in patients with colorectal cancer. Clin Cancer Res. 2021;27(20):5586-5594. [PubMed] [PMC]
3. Tie J, Cohen JD, Lahouel K, et al; DYNAMIC investigators. circulating tumor DNA analysis guiding adjuvant therapy in stage II colon cancer. N Engl J Med. 2022;386(24):2261-2272. [Crossref] [PubMed] [PMC]
4. Kasi PM, Sawyer S, Guilford J, et al. BESPOKE study protocol: a multicentre, prospective observational study to evaluate the impact of circulating tumour DNA guided therapy on patients with colorectal cancer. BMJ Open. 2021;11(9):e047831. [Crossref] [PubMed] [PMC]
5. van der Valk MJM, Hilling DE, Bastiaannet E, et al; IWWD Consortium. Long-term outcomes of clinical complete responders after neoadjuvant treatment for rectal cancer in the International Watch & Wait Database (IWWD): an international multicentre registry study. Lancet. 2018;391(10139):2537-2545. [PubMed]
6. Garcia-Aguilar J, Patil S, Gollub MJ, et al. Organ preservation in patients with rectal adenocarcinoma treated with total neoadjuvant therapy. J Clin Oncol. 2022;40(23):2546-2556. [PubMed] [PMC]
7. Jiang WZ, Xu JM, Xing JD, et al; LASRE trial investigators. Short-term outcomes of laparoscopy-assisted vs open surgery for patients with low rectal cancer: the LASRE randomized clinical trial. JAMA Oncol. 2022;8(11):1607-1615. [PubMed] [PMC]
8. Kobayashi H, Kotake K, Sugihara K, Ajioka Y. Peritoneal lavage cytology in patients with curative resection for stage II and III colorectal cancer: a multi-institutional prospective study. Journal of Clinical Oncology. 2024;42(3_suppl):11. [Crossref]
9. Heinemann V, von Weikersthal LF, Decker T, et al. FOLFIRI plus cetuximab or bevacizumab for advanced colorectal cancer: final survival and per-protocol analysis of FIRE-3, a randomised clinical trial. Br J Cancer. 2021;124(3):587-594. [Crossref] [PubMed] [PMC]
10. Lenz HJ, Van Cutsem E, Luisa Limon M, et al. First-line nivolumab plus low-dose ipilimumab for microsatellite instability-high/mismatch repair-deficient metastatic colorectal cancer: the phase II CheckMate 142 study. J Clin Oncol. 2022;40(2):161-170. [Crossref] [PubMed]
11. André T, Shiu KK, Kim TW, et al; KEYNOTE-177 Investigators. Pembrolizumab in microsatellite-instability-high advanced colorectal cancer. N Engl J Med. 2020;383(23):2207-2218. [Crossref] [PubMed]
12. Diaz LA Jr, Shiu KK, Kim TW, et al; KEYNOTE-177 Investigators. Pembrolizumab versus chemotherapy for microsatellite instability-high or mismatch repair-deficient metastatic colorectal cancer (KEYNOTE-177): final analysis of a randomised, open-label, phase 3 study. Lancet Oncol. 2022;23(5):659-670. [Crossref] [PubMed] [PMC]
13. Kasi PM, Hidalgo M, Jafari MD, et al. Neoadjuvant botensilimab plus balstilimab response pattern in locally advanced mismatch repair proficient colorectal cancer. Oncogene. 2023;42(44):3252-3259. [Crossref] [PubMed] [PMC]
14. Fakih MG, Salvatore L, Esaki T, et al. Sotorasib plus Panitumumab in refractory colorectal cancer with mutated KRAS G12C. N Engl J Med. 2023;389(23):2125-2139. [Crossref] [PubMed]