INTRODUCTION

Colon cancer is the most common gastrointestinal malignancy worldwide, with ~1.15 million new cases diagnosed and 576,858 people dying of colon cancer each year. Currently, surgery, radiotherapy, and systematic chemotherapy are the standard of care for colon cancer patients. Approximately 72% of newly diagnosed colon cancer patients present with local or regional disease, which provides an opportunity for curative-intent treatment. Despite curative surgery and adjuvant chemotherapy, ~30% of patients experience recurrence. The role of adjuvant chemotherapy is to reduce recurrence after curative surgery. The strategy of administering adjuvant chemotherapy has changed dramatically in two decades. The treatment regimen has been established as a combination therapy of 5-fluorouracil/leucovorin (5-FU/LV) and oxaliplatin (FOLFOX), or capecitabine and oxaliplatin (CAPOX). In addition, treatment duration has been investigated in the IDEA collaboration to reduce cumulative peripheral...
sensory neurotoxicity (PSN). However, further studies are needed because some patients have recurrence even if their pathological diagnosis is Stage I, and a certain number of Stage II or Stage III patients have recurrence even though receiving standard adjuvant chemotherapy.

To reduce recurrence, developing new chemotherapeutic agents for adjuvant therapy and stratification of patients are important. There have been many studies that have tried to determine the utility of gene signatures in predicting adjuvant chemotherapy efficacy. However, none of them were able to change the current clinical standards used in selecting an adjuvant treatment for colon cancer. Currently, circulating tumor DNA (ctDNA) is attracting attention as a promising marker of recurrence.

This review presents an overview of published studies on adjuvant chemotherapy and the clinical utility of genetic analysis for the management of patients with localized colon cancer.

2 | HISTORY OF ADJUVANT CHEMOTHERAPY FOR COLON CANCER

2.1 | Standard adjuvant chemotherapy for colon cancer

The National Surgical Adjuvant Breast and Bowel Project (NSABP) C-01 started an adjuvant trial in 1977 (Table 1). This was the first large-scale clinical trial that showed an effect of postoperative adjuvant chemotherapy on survival in colon cancer patients. In the study, 1166 Stage II/III colon cancer patients after curative resection were randomly assigned to three groups: a surgery-alone group, a chemotherapy group (MOF: methyl-CCNU + vincristine + 5-FU), and a BCG (bacillus Calmette–Guérin vaccine) group. Compared with the surgery-alone group, the chemotherapy group showed a significant prolongation in both disease-free survival (DFS) ($P = .02$) and overall survival (OS) ($P = .05$). Subsequently, the NSABP C-03 study was conducted to investigate the utility of 5-FU/LV chemotherapy compared with MOF chemotherapy as the control group. As a result, a significant increased effect of 5-FU/LV compared with MOF was shown for both DFS and OS (5-FU/LV vs MOF, 3-year DFS = 73% vs 64%, $P = .004$, respectively; 3-year OS = 84% vs 77%, $P = .003$, respectively). Furthermore, a randomized controlled trial of the de Gramont regimen (infusional 5-FU) vs the Mayo regimen (bolus 5-FU) for Stage II/III (Dukes B/C) colon cancer patients was conducted by GERCOR, an oncology multidisciplinary research group. Although there were no survival differences, it was shown that the toxicity profile was clearly better in the infusional 5-FU group. Therefore, it was considered that the de Gramont regimen was the most favorable administration method for 5-FU/LV. Since then, it has been shown that oral regimes such as uracil-tegafur (UFT) with LV or capecitabine are equivalent to 5-FU/LV.

After the effects of oxaliplatin, irinotecan, bevacizumab, and antiepidermal growth factor receptor antibodies were examined in patients with recurrent or unresectable colorectal cancer (CRC) a randomized trial comparing combination therapy with these drugs and $5$-FU/LV monotherapy was carried out in the adjuvant setting. In a European and American randomized controlled trial, FOLFOX or CAPOX as postoperative adjuvant chemotherapy for Stage III colon cancer patients resulted in improved recurrence-free survival (RFS) and/or OS. However, the combination of irinotecan with bolus 5-FU/LV (IFL) or irinotecan with folic acid plus infusional $5$-FU (FOLFIRI) was not shown to improve RFS or OS in randomized control trials. Furthermore, in subsequent clinical trials, the addition of molecular targeted drugs such as bevacizumab and cetuximab to FOLFOX or CAPOX did not improve survival outcomes (NSABP C-08 study [FOLFOX ± bevacizumab]; AVANT study [FOLFOX ± bevacizumab, CAPOX ± bevacizumab]; QUASAR-2 study [Capecitabine ± bevacizumab]; N0147 study [FOLFOX ± cetuximab]; and PETACC-8 study [FOLFOX ± cetuximab]). Therefore, the current standard adjuvant chemotherapy for Stage III colon cancer patients is postoperative 6-mo FOLFOX or CAPOX.

For Stage II patients, improvement by adjuvant chemotherapy has not been established compared with Stage III patients. Thus, the recurrence risk of Stage II patients was divided into low, intermediate, and high risk according to the major clinicopathological features, and the patients were treated according to the risk assessment. In the ESMO guideline, <12 lymph nodes examined and T4 tumors are considered important high-risk features, and genetic analysis, which is mentioned later, will be added to the risk assessment in the future. In Japan, the SACURA trial failed to show the superiority of adjuvant tegafur and uracil (UFT) over surgery alone in Stage II colon cancer. However, ad-hoc analysis showed that poorly differentiated patients in the chemotherapy group achieved greater improvement (9.1%) than the surgery-alone group. Additionally, treatment decisions according to risk assessment are deemed necessary and should be established in Asian counties as well as in Western countries.

2.2 | Duration of chemotherapy

Despite the efficacy of FOLFOX or CAPOX chemotherapy for patients with Stage III colon cancer, this treatment leads to significant toxicity. In particular, oxaliplatin-induced cumulative dose-dependent PSN is clinically relevant; therefore, efforts to reduce neurotoxicity have been conducted. Calcium/magnesium and the Japanese herbal medicine Gosha-jinki-gan were found to decrease a neurotoxic symptom in a randomized phase II study. However, in the phase III study, neurotoxicity was shown to increase. It was difficult to lessen oxaliplatin-mediated neurotoxicity even with a combination of a supportive care drug. Therefore, international cooperative clinical trials were conducted to decrease adverse events by shortening the duration of adjuvant chemotherapy treatment. The IDEA (International Duration Evaluation of Adjuvant Chemotherapy) collaboration performed a pooled prospective meta-analysis of individual patient data (IPD) from six concurrently conducted phase III trials carried out at sites in 12 countries to determine whether 3 or 6 mo
### TABLE 1  Pivotal phase III trial for adjuvant chemotherapy in colon cancer

| Study name       | Publication Years | Control vs test arm                  | Sample size | DFS 3 or 5 year (%) | HR  | P      | OS 3 or 5 year (%) | HR  | P      |
|------------------|-------------------|--------------------------------------|-------------|----------------------|-----|--------|-------------------|-----|--------|
| NSABP-C-03      | 1993              | 5-FU/LV                              | 521         | 73 (3 y)             | ND  | .0004  | 71 (3 y)          | ND  | .003   |
|                  |                   | MOF                                 | 524         | 64 (3 y)             |     |        | 55 (3 y)          |     |        |
| Andre T et al   | 2003              | LV5FU2 (noninferiority)              | 452         | 73 (3 y)             | 1.04| .74    | 86 (3 y)          | 1.26| .18    |
| Mayo regimen     |                   | LV5FU2 (noninferiority)              | 453         | 72 (3 y)             |     |        | 87 (3 y)          |     |        |
| NSABP C-06      | 2005              | UFT/LV (noninferiority)              | 551         | 77.8 (5 y)           | 1.004| .0236  | 87.5 (5 y)        | 1.014| ND     |
|                  |                   | 5-FU/LV(RPMI)                        | 550         | 79.3 (5 y)           |     |        | 88.4 (5 y)        |     |        |
| X-ACT           | 2005              | Capecitabine (noninferiority)        | 1004        | 65.5 (3 y)           | 1.06| P < .001 | 81.3 (3 y)        | 0.84| .05    |
|                  |                   | 5-FU/LV(RPMI)                        | 983         | 61.9 (3 y)           |     |        | 77.6 (3 y)        |     |        |
| MOSAIC           | 2009              | FOLFOX4                              | 1123        | 73.3 (5 y)           | 0.80| .003   | 78.5 (6 y)        | 0.84| .046   |
|                  |                   | LV5FU2                               | 1123        | 67.4 (5 y)           |     |        | 76.0 (6 y)        |     |        |
| NSABP C-07      | 2011              | FLOX                                 | 1209        | 69.4 (5 y)           | 0.82| .002   | 80.2 (5 y)        | 0.88| .08    |
|                  |                   | 5-FU/LV (RPMI)                       | 1200        | 64.2 (5 y)           |     |        | 78.4 (5 y)        |     |        |
| NO16968/       | 2015              | CAPOX                                | 944         | 63 (7 y)             | 0.80| .004   | 73 (7 y)          | 0.83| .04    |
| XELOXA          |                   | 5-FU/LV (Mayo or RPMI)               | 942         | 56 (7 y)             |     |        | 67 (7 y)          |     |        |
| CALGB 89803     | 2007              | IFL                                  | 635         | 61 (5 y)             | ND  | .85    | 68 (5 y)          | ND  | .74    |
|                  |                   | RPMI                                 | 629         | 59 (5 y)             |     |        | 71 (5 y)          |     |        |
| PETACC-3       | 2009              | FOLFIRI                              | 1050        | 56.7 (3 y)           | 0.86 (adjusted) | .106 | 73.6 (3 y)        | 0.83 (adjusted) | .094 |
|                  |                   | LV5FU2                               | 1044        | 54.3 (3 y)           |     |        | 71.3 (3 y)        |     |        |
| NSABP C08      | 2011              | mFOLFOX6 + Bevacizumab               | 1334        | 77.4 (3 y)           | 0.89| .15    | -                | -   | -      |
|                  |                   | mFOLFOX6                             | 1338        | 75.6 (3 y)           |     |        | -                | -   | -      |
| AVANT           | 2012              | A: mFOLFOX6 + Bevacizumab            | 955         | 76 (3 y)             | 1.17| (A vs C) | .443 (A vs C)   | -   | 1.27 (A vs C) | .02 |
|                  |                   | B:CAPOX + Bevacizumab                | 960         | 73 (3 y)             |     |        | -                | -   |        |
|                  |                   | C:mFOLFOX6                           | 952         | 75 (3 y)             |     |        | -                | -   |        |
| QUASAR 2       | 2016              | Capecitabine + Bevacizumab           | 973         | 75.4 (3 y)           | 1.06| .54    | 87.5 (3 y)        | 1.11| .33    |
|                  |                   | Capecitabine                         | 968         | 78.4 (3 y)           |     |        | 89.4 (3 y)        |     |        |
| PETACC-8       | 2014              | FOLFIRI + Cetuximab                  | 791         | 75.1 (3 y)           | 1.05| .6562  | 88.3 (3 y)        | 1.09| .5583  |
|                  |                   | FOLFIRI                              | 811         | 78.0 (3 y)           |     |        | 90.5 (3 y)        |     |        |

Abbreviations: CAPOX, capecitabine/oxaliplatin; DFS, disease-free survival; FOLFIRI, irinotecan/leucovorin/5FU; FOLFOX, oxaliplatin/leucovorin/5FU; HR, hazard ratio; LV5FU2, leucovorin/infusional 5-FU; MOF, methyl-CCNU/Vincristine/5-FU; ND, not determined; OS, overall survival; P, probability.

*Noninferiority test.
of therapy altered DFS 3 years after therapy with either FOLFOX or CAPOX. This study included 12,834 patients who fulfilled the criteria and who were randomly divided into 3- or 6-mo adjuvant chemotherapy duration groups. A shorter duration of adjuvant therapy was associated with significantly lower rates of adverse events than a longer duration, which was not related to the chemotherapy regimen. Neurotoxicity of grade 2 or higher was significantly lower in the 3-mo (16.6% in FOLFOX and 14.2% in CAPOX) than in the 6-mo therapy group (47.7% in FOLFOX and 44.9% in CAPOX). However, the noninferiority of 3 mo in comparison with 6 mo of treatment was not elucidated in the modified intention-to-treat (mITT) population (hazard ratio [HR]: 1.07; 95% confidence interval [CI]: 1.00–1.15 [the upper limit CI cutoff being 1.12]); it was confirmed only with CAPOX (HR: 0.95; 95% CI: 0.85–1.06) but not with FOLFOX (HR: 1.16; 95% CI: 1.06–1.26). Three months of therapy was noninferior to 6 mo in patients with T1, T2, or T3 and N1 cancers (HR, 1.01; 95% CI, 0.90–1.12) in an exploratory analysis. In patients with cancers classified as T4 and/or N2, the DFS rate in the 6-mo adjuvant chemotherapy duration was superior to the 3-mo adjuvant chemotherapy duration group (64.4% vs 62.7%) (HR, 1.12; 95% CI, 1.03–1.23; P = .01 for superiority). In the final analysis with a median follow-up of 72.3 mo, noninferiority was not statistically proved in the mITT population. However, the absolute difference in median OS was 0.4% between the 3- and 6-mo groups. It was important that the neurotoxicity was clearly decreased. Therefore, the study group concluded that 3 mo of CAPOX treatment was clinically acceptable. In the American Society of Clinical Oncology, the European Society for Medical Oncology, and the Japanese Society of Medical Oncology guidelines, 3 mo of CAPOX therapy is recommended for low-risk Stage III (T1-3 and N1) colon cancer patients, while it is considered an option for those with high-risk Stage III (T4 and/or N2) disease.

3 | RISK STRATIFICATION OF COLON CANCER PATIENTS

3.1 | Microsatellite instability (MSI)

Microsatellite instability is found in approximately 10%–20% of Stage II/III and 3% of Stage IV colon cancer patients. MSI characterizes tumors with deficient DNA mismatch repair (dMMR) associated with loss of function (because of mutation or silencing) of one of the four DNA mismatch repair genes: MLH1, MSH2, MSH6, or PMS2. MSI is used clinically as a molecular marker for screening of Lynch syndrome and has a role as a prognostic marker in Stage II and III colon cancer. MSI status is also considered an important biomarker when selecting patients for adjuvant chemotherapy. Ribic et al first showed the relationship between patients with Stage II and III colon cancer and microsatellite status using data from clinical trials. All patients received 5-FU-based adjuvant chemotherapy; however, those who were low MSI/microsatellite stable had a better OS than those who were MSI-H. Many studies have demonstrated a predictive role for dMMR/MSI-H in patients treated with 5-FU-based adjuvant chemotherapy regimens, and Stage II colon cancer patients who are dMMR/MSI-H do not benefit from 5-FU-based adjuvant chemotherapy. Therefore, treating Stage II patients who are MSI-H with adjuvant chemotherapy should be avoided. However, the MOSAIC (Multicenter International Study of Oxaliplatin/Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer) study, after a 10-year follow-up, found that FOLFOX-4 was associated with better OS (HR, 0.41) compared with LV5FU2 in MSI-H, Stage III colon cancer patients. The ACCENT clinical trial database also showed that adding oxaliplatin to fluoropyrimidine improves OS and DFS in patients with MSI low-risk Stage III colon cancer.

3.2 | BRAF V600E mutation

BRAF mutations are present in 5% of CRC patients. More than 80% of mutations are found at the V600E position, with valine (V) changed to glutamic acid (E) and transversion of the 1799th T to an A at codon 600. During classification of intrinsic subtypes in CRC, the BRAF mutation and MSI-H are sometimes categorized into the same group. The reason is that MSI-H tumors often contain a BRAF mutation, except in patients with Lynch syndrome, because the BRAF mutation, MSI-H, and genome-wide DNA methylation (CpG islands methylated phenotype: CIMP) are strongly related. Therefore, BRAF V600E mutations as a predictive biomarker in the adjuvant setting is unclear. Many retrospective studies showed that colon cancer patients with a BRAF mutation have a poor prognosis even after curative resection. The presence of BRAF mutations was found to reduce patient survival in Stage III and IV but not Stage II CRC. Although larger studies are needed, many previous studies did not include Stage I/II colon cancer patients. In addition, 30% of colon cancer patients with a BRAF mutation are MSI-H, and MSI-H have good outcomes even in cases with a BRAF mutation.

3.3 | RAS mutations

In CRC patients, RAS mutations are present in 45% of Stage IV and approximately 20%–40% of Stage II/III tumors, and they are more often found in MSS compared with MSI colorectal tumors. There have been many reports demonstrating the prognostic value of RAS mutation status. Large post-hoc analysis of data collected from adjuvant clinical studies including NO147 and PETACC-8 has found that RAS was a prognostic marker in MSS but not in MSI patients. However, the results were conflicting, with some studies reporting a poor prognostic impact of RAS mutations and others suggesting no prognostic value. MSI-H tumors are located in the proximal colon in the majority of cases. Therefore, the KRAS gene might only be associated with a worse prognosis in patients with a distal tumor. For Stage II patients, the presence of clinical high-risk features (poorly differentiated histology, vascular invasion, perineural invasion, examination of <12 lymph nodes, bowel obstruction, or localized perforation) have been used in the selection
of adjuvant chemotherapy. Currently, the MSI, RAS, and BRAF mutation status may help stratify patients with these clinical features. MSI status is the first selection criterion, and patients may be stratified using their BRAF/RAS mutation status if the patient is MSS with clinical high-risk features.

### 3.4 | Gene signatures

To date, some multigene assay systems have been developed to evaluate recurrence risk in patients with CRC, which are independent of currently used prognostic parameters (Table 2). The Oncotype DX Recurrence Score (RS) developed by Genomic Health is a quantitative reverse transcription polymerase chain reaction (RT-qPCR) assay using RNA extracted from formalin-fixed, paraffin-embedded (FFPE) tumor tissue to assess recurrence risk in Stage II/III colon cancer patients. This assay has been validated in Stage II and III colon cancer without chemotherapy in Western countries, Korea, and Japan. In a Japanese study, a cohort sampling design was employed, and 630 Stage II/III patients treated with surgery alone were sampled with a 1:2 ratio of recurrence to nonrecurrence. Association of RS with the recurrence-free interval was assessed using weighted Cox regression. The patients in the Oncotype DX high-risk Stage II group had a 5-year risk of recurrence similar to patients with Stage IIIA/IIIB disease in the low-risk group (19% vs 20%), and Stage IIIA/IIIB patients in the high-risk group showed similar RSs to that of Stage IIIC patients in the low-risk group.

ColDx (Almac, Craigavon, UK) is a microarray-based 634-transcript gene signature that identifies high-risk and low-risk Stage II colon cancer patients after surgery using FFPE samples. Similar to the Oncotype DX Colon Cancer assay, the ColDx assay uses FFPE tissue, which has the benefit that the test can be performed on archived samples rather than on fresh tissue. In the validation study, the signature predicted 5-year RFS of ~70% in the low-risk group and 40% in the high-risk group (HR: 2.53; 95% CI: 1.54–4.15; P < .001). The disadvantage of ColDx is that there have been few validation studies performed to date.

ColoPrint developed by Agendia (Irvine, CA) is an 18-gene prognostic classifier that involves performing RT-PCR on fresh frozen tumor tissue obtained during surgery to determine survival risk. This signature was validated in patients with Stage I, II, and III disease. This signature classified 60% patients as low risk for recurrence and 40% as high risk for recurrence with a 5-year RFS rate of 87.6% and 67.2%, respectively. A prospective clinical validation study in Stage II and III patients is underway at the MD Anderson Cancer Institute, and an international Prospective Assessment of Risk Stratification of ColoPrint (PARSC) study of 575 patients is also underway in Stage II and III patients in the United States, Asia, and Europe.

Consensus molecular subtypes (CMSs) for CRC that include over 600 genes were first reported by Guinney et al. The classifier allowed characterization of the originally unlabeled samples from a network analysis. The CMS was generated by an international consortium with large-scale data sharing from several gene signature analyses, and consists of four CMSs with distinguishing features: CMS1 (MSI immune, 14%), hypermutated, microsatellite unstable, and strong immune activation; CMS2 (canonical, 37%), epithelial, and marked WNT and MYC signaling activation; CMS3 (metabolic, 13%), epithelial and evident metabolic dysregulation; and CMS4 (mesenchymal, 23%), prominent transforming growth factor β activation, stromal invasion, and angiogenesis. The CMS1 tumors were frequently diagnosed in females with right-sided lesions, and the CMS1 patients showed good RFS but had a very poor survival rate after relapse in comparison with other subtypes. CMS may be a prognostic or predictive biomarker for adjuvant chemotherapy in Stage II/III CRC. However, a microarray-based system is not practical for daily use because of the difficulty in preparing samples for RNA extraction. The use of an analytical system that reduced the number of the genes required has been reported recently. A 55-gene classifier (55GC) and RAS mutations in colon cancer are being validated in resected Stage II/III patients treated with adjuvant chemotherapy in Japan.

#### 3.5 | Immunoscore

The tumor microenvironment and immune cell infiltration have been shown to have predictive and prognostic value rather than the classic pathological criteria, including T and N stage or metastatic status. The Immunoscore relies on the quantification of lymphocyte populations, especially CD3- and CD8-positive T cells in the tumor

| Table 2 Overview of four gene signatures and the Immunoscore |
|-----------------------------------------------|
| **Assay** | **Gene characteristics** | **Method** | **Requirement** |
| Oncotype DX | 12 gene (7 prognostic genes and 5 reference genes) | RT-PCR | Formalin-fixed paraffin embedded tissue |
| ColoPrint | 18 genes | RT-PCR | Fresh-frozen tissue |
| ColDX | 634 genes | Microarray | Fresh-frozen tissue or formalin-fixed paraffin embedded tissue |
| Curebest 55GC Colon | 55 genes selected from Microarray | Microarray | Formalin-fixed paraffin embedded tissue |
| Immunoscore | Proportion of CD3- and CD8-positive T cells | Immunohistochemistry | Formalin-fixed paraffin embedded tissue |

Abbreviations: RT-PCR, reverse transcription real-time polymerase chain reaction.
center and the invasive margin. This system was developed using an automated digital imaging system controlled via dedicated software (Immunoscore Analyzer, HalioDx, Richmond, VA). A worldwide Immunoscore consortium identified a strategy to demonstrate the feasibility and reproducibility of the Immunoscore, and it validated its major prognostic power in colon cancer Stage I/II/III patients. The Immunoscore was shown to contribute the most to determining risk among all clinical parameters; therefore, the Immunoscore may be integrated into TNM staging as TNM-I in the clinical setting in Western countries. Immunoscore has demonstrated benefits in determining the risk of recurrence for Stage II patients in addition to the pathological features. However, its role in predicting chemotherapy benefit remains uncertain.

3.6 | ctDNA

tDNA is derived from cancer cells and released into the bloodstream as a result of tumor cell necrosis. ctDNA represents only a small fraction of circulating DNA, but this fraction is highly variable, ranging from less than 0.1% to greater than 10% depending on tumor stage, disease burden, biologic shedding, or proliferation, and on atomic factors such as disease site.

Once in the circulation, ctDNA is cleared rapidly from the bloodstream with a half-life of approximately 2 h. ctDNA can be found in both the early stage and metastatic disease across different solid tumor types, but the detection rate varies between tumor types and different stages of the same tumor type. Recently, a novel technology for detecting minimal residual disease using ctDNA has been discovered. Tie et al reported that ctDNA was detected postoperatively in 14 of 178 (7.9%) patients, 11 (79%) of whom developed recurrence at a median follow-up of 27 mo. Recurrence occurred in only 16 (9.8%) of 164 patients with negative ctDNA (HR: 18, 95% CI: 7.9–40) in patients not treated with adjuvant chemotherapy. Another report also showed that ctDNA-positive patients at postoperative day 30 were 7.2 times more likely to relapse than ctDNA-negative patients, in Stage II/III patients. Currently, new prospective studies are in progress all over the world. In Japan, nationwide large-scale clinical trials have already been initiated. CIRCULATE-Japan consists of a prospective observational study and two accompanying interventional studies. Clinical Stage II–III as well as R0-intent Stage IV patients are being enrolled. The sample size of the observational study named GALAXY is 5000, and ctDNA will be analyzed at regular timepoints pre- and post-surgery over a 2-year period using the Signatera (Natera, San Carlos, CA) system. High-risk Stage II/low-risk Stage III patients who are ctDNA-negative at 4-week post-surgery will be included in the interventional study named the VEGA trial, which is a phase III study comparing surgery alone with adjuvant 4-cycle CAPOX. Studies for ctDNA-negative patients will be included in a prospective meta-analysis as the global CIRCULATE IDEA project, which will be conducted in more than 10 countries. As part of the CIRCULATE-Japan platform, a randomized phase III trial named ALTAIR will be performed to compare an investigational new drug with a placebo in patients who are ctDNA-positive at any timepoint even though they have been treated with standard adjuvant chemotherapy. Approximately 150 institutions across Japan and Taiwan are joining in the CIRCULATE-Japan project. Currently, postoperative (4 weeks) ctDNA-positive status was detected in 18% (140/797) of the patients, with 5% (3/66), 5% (15/278), 25% (74/301), and 32% (48/152) in pStage I, II, III, and IV, respectively, in the GALAXY study by Shiras H et al, which was reported in the ESMO World Congress on Gastrointestinal Cancer 2021.

4 | SUMMARY

The purpose of adjuvant postoperative treatment is to prevent recurrence in colon cancer patients. Until now, efforts to maximize drug intensity for adjuvant chemotherapy have been pursued. In future research, it is important to stratify patients using genomic analysis. ctDNA may be the most promising method among the various genomic tests to optimally risk-stratify patients. Sustainable research and development of more efficacious adjuvant treatments and prognostic/predictive stratification assays are necessary to generate the ultimate colon cancer therapy.

ACKNOWLEDGMENT

We thank Mark Abramovitz, PhD, from Edanz (https://jp.edanz.com/ac) for editing a draft of this article.

DISCLOSURE

Eiji Oki received lecture fees from Taiho and Chugai. Hiroya Taniguchi received lecture fees from Taiho and Chugai. Takayuki Yoshino received lecture fees from Taiho and Chugai, and research funds from Taiho and Chugai. Masaki Mori received research funds from Taiho and Chugai, and received a lecture fee from Taiho and Chugai.

ORCID

Eiji Oki https://orcid.org/0000-0002-9763-9366

REFERENCES

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71:24–43.
2. Siegel RL, Miller KD, Goding Sauer A, Fedewa SA, Butterly LF, Anderson JC, et al. Colorectal cancer statistics, 2020. CA Cancer J Clin. 2020;70:145–64. https://doi.org/10.3322/caac.21601. Epub 2020 Mar 5
3. André T, Boni C, Navarro M, Tabernero J, Hickish T, Topham C, et al. Improved overall survival with oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment in stage II or III colon cancer in the MOSAIC trial. J Clin Oncol. 2009;27:3109–16. https://doi.org/10.1200/JCO.2008.20.6771. Epub 2009 May 18
4. Kuebler JP, Wieand HS, O’Connell MJ, Smith RE, Colangelo LH, Yotthons G, et al. Oxaliplatin combined with weekly bolus fluorouracil and leucovorin as surgical adjuvant chemotherapy for stage II and III colon cancer: results from NSABP C-07. J Clin Oncol. 2007;25:2198–204. https://doi.org/10.1200/JCO.2006.08.974. Epub 7 Apr 30
5. André T, Iveson T, Labianca R, Meyerhardt JA, Souglakos I, Yoshino T, et al. The IDEA (international duration evaluation of adjuvant chemotherapy) collaboration: prospective combined analysis of phase III trials investigating duration of adjuvant therapy with the FOLFOX (FOLFOX4 or Modified FOLFOX6) or XELOX (3 versus 6 month) regimen for patients with stage III colon cancer: trial design and current status. Curr Colorectal Cancer Rep. 2011;9:261–9. https://doi.org/10.1007/s11888-013-0181-6

6. Gill S, Meyerhardt JA, Arun M, Veenstra CM. Translating IDEA to practice and beyond: managing stage II and III colon cancer. Am Soc Clin Oncol Educ Book. 2019;39:226–35. https://doi.org/10.1200/EDBK_237443. Epub 2019 May 17

7. Puccini A, Berger MD, Zhang W, Lenz HJ. What we know about stage II and III colon cancer: it’s still not enough. Target Oncol. 2017;12:265–75. https://doi.org/10.1007/s11761-017-0494-5

8. Chakrabarti S, Xie H, Urrutia R, Mahipal A. The promise of circulating tumor DNA (ctDNA) in the management of early stage colon cancer: a critical review. Cancers (Basel). 2020;12:2808. https://doi.org/10.3390/cancers12102808

9. Reinert T, Henriksen TV, Christensen E, Sharma S, Sarai R, Sethi H, et al. Analysis of plasma cell-free DNA by ultra-deep sequencing in patients with stages I to III colorectal cancer. JAMA Oncol. 2019;5:1124–31. https://doi.org/10.1001/jamaoncol.2019.0528

10. Wolmark N, Fisher B, Rockette H, Redmond C, Wickerham DL, Fisher ER, et al. Postoperative adjuvant chemotherapy or BCG for colon cancer: results from NSABP protocol C-01. J Natl Cancer Inst. 1988;80:30–6. https://doi.org/10.1093/jnci/80.1.30

11. Wolmark N, Rockette H, Fisher B, Wickerham DL, Redmond C, Fisher ER, et al. The benefit of leucovorin-modulated fluorouracil as postoperative adjuvant therapy for primary colon cancer: results from National Surgical Adjuvant Breast and Bowel Project protocol C-03. J Clin Oncol. 1993;11:1879–87. https://doi.org/10.1200/JCO.1993.11.10

12. Andre T, Colin P, Louvet C, Gamelin E, Bouche O, Achille E, et al. Semimonthly versus monthly regimen of fluorouracil and leucovorin administered for 24 or 36 weeks as adjuvant therapy in stage II and III colon cancer: results of a randomized trial. J Clin Oncol. 2003;21:2896–903. https://doi.org/10.1200/JCO.2003.0.065

13. Lembersky BC, Wieand HS, Petrelli NJ, O’Connell MJ, Colangelo LH, Smith RE, et al. Oral uracil and tegafur plus leucovorin compared with intravenous fluorouracil and leucovorin in stage II and III carcinoma of the colon: results from National Surgical Adjuvant Breast and Bowel Project Protocol C-06. J Clin Oncol. 2006;24:2059–64. https://doi.org/10.1200/JCO.2005.04.7498

14. Twelves C, Wong A, Nowacki MP, Abt M, Burris H 3rd, Carrato A, et al. Prospective multicenter study on the prognostic and predictive impact of tumor budding in stage II colon cancer: results from the SOUTEC trial. J Clin Oncol. 2017;35:1886–94. https://doi.org/10.1200/JCO.2016.70.1660. Epub 2017 Jun 28

15. Oki E, Emi Y, Kojima H, Higashijima J, Kato T, Miyake Y, et al. Prevention of Goshajinkigan to prevent oxaliplatin-induced neuropathy. Cancer Chemother Pharmacol. 2013;72:1283–90. https://doi.org/10.1007/s00280-013-2306-7

16. Grothey A, Nikcevich DA, Sloan JA, Kugler JW, Silverstein PT, Dentchev T, et al. Intravenous calcium and magnesium for oxaliplatin-induced sensory neurotoxicity in adjuvant colon cancer: NCCTG N04C7. J Clin Oncol. 2011;29:421–7. https://doi.org/10.1200/JCO.2010.30.0855. Epub 2010 Dec 28

17. Oki E, Emi Y, Kojima H, Higashijima J, Kato T, Miyake Y, et al. Preventive effect of Goshajinkigan on peripheral neurotoxicity of FOLFOX therapy (GENIUS trial): a placebo-controlled, double-blind, randomized phase III study. Int J Clin Oncol. 2015;20:767–75. https://doi.org/10.1007/s10147-015-0784-9. Epub 2015 Jan 28

18. Van Cutsem E, Labianca R, Bodoky G, Barone C, Aranda E, Nordlinger B, et al. Randomized phase III trial comparing biweekly infusional fluorouracil/leucovorin alone or with irinotecan in the adjuvant treatment of stage III colon cancer: PETACC-3. J Clin Oncol. 2009;27:3117–25. https://doi.org/10.1200/JCO.2009.21.6663. Epub 2009 May 18

19. B, et al. Effect of duration of adjuvant chemotherapy for patients with stage III colon cancer (IDEA collaboration): final results from a prospective, pooled analysis of six randomised, phase 3 trials. Lancet Oncol. 2020;21:1620–9. https://doi.org/10.1016/S470-2045(20)30527-1
31. Yoshino T, Kotaka M, Shinzaki K, Touyama T, Manaka D, Matsui T, et al. JOIN trial: treatment outcome and recovery status of peripheral sensory neuropathy during a 3-year follow-up in patients receiving modified FOLFOX6 as adjuvant treatment for stage II/III colon cancer. Cancer Chemother Pharmacol. 2019;84:1269–77. https://doi.org/10.1007/s00280-019-3957-5. Epub 2019 Sep 23

32. Taieb J, Shi Q, Pederson L, Alberts S, Wolmark N, Van Cutsem E, et al. Prognosis of microsatellite instability and/or mismatch repair deficiency stage III colon cancer patients after disease recurrence following adjuvant treatment: results of an ACCENT pooled analysis of seven studies. Ann Oncol. 2019;30:1466–71. https://doi.org/10.1093/annonc/mdz208

33. Ribic CM, Sargent DJ, Moore MJ, Thibodeau SN, French AJ, Taieb J, Shi Q, Pederson L, Alberts S, Wolmark N, Van Cutsem E, et al. Prognosis of microsatellite instability and/or mismatch repair deficiency stage III colon cancer patients after disease recurrence following adjuvant treatment: results of an ACCENT pooled analysis of seven studies. Ann Oncol. 2019;30:1466–71. https://doi.org/10.1093/annonc/mdz208

34. Carethers JM, Smith EJ, Behling CA, Nguyen L, Taima A, Doctolero RT, et al. Use of 5-fluorouracil and survival in patients with microsatellite-unstable colorectal cancer. Gastroenterology. 2004;126:394–401. https://doi.org/10.1053/j.gastro.2003.12.023

35. Sargent DJ, Marsoni S, Monges G, Thiodeau SN, Labianca R, Hamilton SR, et al. Defective mismatch repair as a predictive marker for lack of efficacy of fluorouacil-based adjuvant chemotherapy for colon cancer. J Clin Oncol. 2010;28:3219–26. https://doi.org/10.1200/JCO.2009.27.1825. Epub 2010 May 24

36. Sinicrope FA, Foster NR, Thiodeau SN, Marsoni S, Monges G, Labianca R, et al. DNA mismatch repair status and colon cancer recurrence and survival in clinical trials of 5-fluorouracil-based adjuvant therapy. J Natl Cancer Inst. 2011;103:863–75. https://doi.org/10.1093/jnci/dj153. Epub 2011 May 19

37. Sinicrope FA, Shi Q, Allegra CJ, Smyrk TC, Thiodeau SN, Goldberg RM, et al. Association of DNA mismatch repair and mutations in BRAF and KRAS with survival after recurrence in stage III colon cancers: a secondary analysis of 2 randomized clinical trials. JAMA Oncol. 2017;3:472–80. https://doi.org/10.1001/jamaoncol.2016.5469

38. Cohen R, Taieb J, Fiskum J, Ythors G, Goldberg R, Yoshino T, et al. Microsatellite instability in patients with stage III colon cancer receiving fluoropyrimidine with or without oxaliplatin: an ACCENT pooled analysis of 12 adjuvant trials. J Clin Oncol. 2021;39:642–51. https://doi.org/10.1200/JCO.2020.39.15_suppl.295136. Epub 2021 Mar 3

39. Ogino S, Shima K, Meyerhardt JA, McCleary NJ, Ng K, Hollis D, et al. Mutations of BRAF are associated with extensive hMLH1 promoter methylation in sporadic colorectal cancer. Int J Cancer. 2004;108:237–42. https://doi.org/10.1002/ijc.11123

40. Nakaji Y, Oki E, Nakashima K, Ando K, Sugiyama M, Nakashima Y, et al. Prognostic value of BRAF V600E mutation and microsatellite instability in Japanese patients with sporadic colorectal cancer. J Cancer Res Clin Oncol. 2017;143:151–60.
Colon Cancer Assay) in Korean patients with stage II colon cancer: implication of ethnic differences contributing to differences in gene expression. Onco Targets Ther. 2015;8:3817-25. https://doi.org/10.2147/OTT.S59543. eCollection 2015

58. Kennedy RD, Bylesjo M, Kerr P, Davison T, Black JM, Kay EW, et al. Development and independent validation of a prognostic assay for stage II colon cancer using formalin-fixed paraffin-embedded tissue. J Clin Oncol. 2011;29:4620-6. https://doi.org/10.1200/JCO.2011.35.4498. Epub 2011 Nov 7

59. Niedzwiecki D, Frankel WL, Venook AP, Ye X, Friedman PN, Goldberg RM, et al. Association between results of a gene expression signature assay and recurrence-free interval in patients with stage II colon cancer in colon and leukemia group B 9581 (Alliance). J Clin Oncol. 2016;34:3047-53. https://doi.org/10.1200/JCO.2015.65.4699. Epub 2016 Jul 18

60. Tan IB, Tan P. Genetics: an 18-gene signature (ColoPrint) for colon cancer prognosis. Nat Rev Clin Oncol. 2011;8:131–3. https://doi.org/10.1038/nrclinonc.2010.229. Epub 2010 Feb 8

61. Kopetz S, Tabernero J, Rosenberg R, Jiang ZQ, Moreno V, Bachleitner-Hofmann T, et al. Genomic classifier ColoPrint predicts recurrence in stage II colorectal cancer patients more accurately than clinical factors. Oncologist. 2015;20:127–33. https://doi.org/10.1634/theoncologist.2014-0325. Epub 2015 Jan 5

62. Salazar R, Roepman P, Capella G, Moreno V, Simon I, Dreezen C, et al. Gene expression signature to improve prognostic prediction of stage II and III colorectal cancer. J Clin Oncol. 2011;29:17-24. https://doi.org/10.1200/JCO.2010.30.1077. Epub 2010 Nov 22

63. Salazar R, Willem de Waard J, Glimelius B, Marshall J, Klaase J, Van Der Hoeven J, et al. The PARSC trial, a prospective study for the assessment of recurrence risk in stage II colon cancer (CC) patients using ColoPrint. J Clin Oncol. 2012;30(4_suppl):678-_.

64. Guinney J, Dienstmann R, Wang X, de Reyniès A, Schlicker A, Soneson C, et al. The consensus molecular subtypes of colorectal cancer. Nat Med. 2015;21:1350–6. https://doi.org/10.1038/nm.3967. Epub 2015 Oct 12

65. Li Y, Yao Q, Zhang L, Mo S, Cai S, Huang D, et al. Immunohistochemistry-based consensus molecular subtypes as a prognostic and predictive biomarker for adjuvant chemotherapy in patients with stage II colorectal cancer. Oncologist. 2020;25:e1968-e79. https://doi.org/10.1002/ONCO.13521. Epub 2020 Sep 28

66. Kwon Y, Park M, Jang M, Yun S, Kim WK, Kim S, et al. Prognosis of stage III colorectal carcinomas with FOLFOX adjuvant chemotherapy can be predicted by molecular subtype. Oncotarget. 2017;8:39367-81. https://doi.org/10.18632/oncotarget.7023

67. Song N, Pogue-Geile KL, Gavin PG, Yothers G, Kim SR, Johnson NL, et al. Clinical outcome from oxaliplatin treatment in stage II/III colon cancer according to intrinsic subtypes: secondary analysis of NSABP C-07/NRG oncology randomized clinical trial. JAMA Oncol. 2016;2:1162-9. https://doi.org/10.1001/jamaoncol.2016.314

68. Shimoto E, Oki E, Shimokawa M, Yamaguchi S, Ishiguro M, Morita M, et al. A validation study for recurrence risk stratification of stage II colon cancer using the 55-gene classifier. Oncology. 2020;1:1-8.

69. Galon J, Costes A, Sanchez-Cabo F, Kirilovsky A, Mlecnik B, Lagorce-Pagès C, et al. Type, density, and location of immune cells within human colorectal tumors predict clinical outcome. Science. 2006;313:1960-4. https://doi.org/10.1126/science.1129139

70. Galon J, Fridman WH, Pagès F. The adaptive immunologic microenvironment in colorectal cancer: a novel perspective. Cancer Res. 2007;67:1883–6. https://doi.org/10.1158/0008-5472.CAN-06-4806

71. Pagès F, Mlecnik B, Marliot F, Bindea G, Ou FS, Bifulco C, et al. International validation of the consensus Immunoscore for the classification of colon cancer: a prognostic and accuracy study. Lancet. 2018;391:2128-39. https://doi.org/10.1016/S0140-6736(18)30789-X. Epub 2018 May 10

72. Dasari A, Morris VK, Allegra CJ, Atreyea C, Benson AB 3rd, Boland P, et al. ctDNA applications and integration in colorectal cancer: an NCI Colon and Rectal-Anal Task Forces whitepaper. Nat Rev Clin Oncol. 2020;17:757-70. https://doi.org/10.1038/s41571-020-0392-0. Epub 2020 Jul 6

73. Tie J, Wang Y, Tomasetti C, Li L, Springer S, Kinde I, et al. Circulating tumor DNA analysis detects minimal residual disease and predicts recurrence in patients with stage II colon cancer. Sci Transl Med. 2016;8:346ra92. https://doi.org/10.1126/scitranslmed.aaf6219

74. Schraa SJ, van Rooijen KL, van der Kruisjes DEW, Rubio Alarcón C, Phallen J, Sausen M, et al. Circulating tumor DNA guide adjuvant chemotherapy in stage II colon cancer (MEDOCC-CrEATE): study protocol for a trial within a cohort study. BMC Cancer. 2020;20:790. https://doi.org/10.1186/s12885-020-07252-y

75. Parikh AR, Van Seventer EE, Siravegna G, Hartwig AV, Jaivinich A, He Y, et al. Minimal residual disease detection using a plasma-only circulating tumor DNA assay in colorectal cancer patients. Clin Cancer Res. 2021;29:1078-0432.

76. Tie J, Cohen JD, Wang Y, Christie M, Simons K, Lee M, et al. Circulating tumor DNA analyses as markers of recurrence risk and benefit of adjuvant therapy for stage III colon cancer. JAMA Oncol. 2019;5:1710–7. https://doi.org/10.1001/jamaoncol.2019.3616

77. Reinert T, Schaler LV, Thomsen R, Tobiasen H, Vang S, Nordenstof F, et al. Analysis of circulating tumor DNA to monitor disease burden following colorectal cancer surgery. Gut. 2016;65:625–34. https://doi.org/10.1136/gutjnl-2014-308859. Epub 2015 Feb 4

78. Taniguchi H, Nakamura Y, Kotani D, Yuki H, Mishima S, Sawada K, et al. CIRCULATE-Japan: Circulating tumor DNA-guided adaptive platform trials to refine adjuvant therapy for colorectal cancer. Cancer Sci. 2021;1:14926.

79. Yothers G, O’Connell MJ, Allegra CJ, Kuebler JP, Colangelo LH, Petrelli NJ, et al. Oxaliplatin as adjuvant therapy for colon cancer: updated results of NSABP C-07 trial, including survival and subset analyses. J Clin Oncol. 2011;29:3768-74. https://doi.org/10.1200/JCO.2011.36.4539. Epub 2011 Aug 22

80. Schmoll HJ, Tabernero J, Maroun J, de Braud F, Price T, Van Cutsem E, et al. Capecitabine Plus oxaliplatin compared with fluorouracil/folinic acid as adjuvant therapy for stage III colon cancer: final results of the NO16968 randomized controlled phase III trial. J Clin Oncol. 2015;33:3733-40. https://doi.org/10.1200/JCO.2015.60.9107. Epub 2015 Aug 31