Phase II study of an oxaliplatin-based regimen for relapsed colon cancer patients treated with oxaliplatin-based adjuvant chemotherapy (INSPIRE study)

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Abstract
Background The aim of this study was to evaluate the efficacy and safety of first-line chemotherapy with re-introduction of oxaliplatin (OX) more than 6 months after adjuvant chemotherapy including OX.

Methods Stage II/III colon cancer patients with neuropathies of grade ≤ 1 who relapsed more than 6 months after adjuvant chemotherapy including OX were considered eligible. Eligible patients were treated with 5-fluorouracil, L-leucovorin and OX plus molecularly targeted agents or capecitabine and OX plus bevacizumab (BV) or S-1 and OX plus BV. The primary endpoint was the progression-free survival (PFS), and the secondary endpoints were the overall survival (OS), response rate (RR) and toxicity.

Results A total of 50 patients were enrolled between September 2013 and May 2019. Twelve patients received 5-fluorouracil, L-leucovorin and OX (FOLFOX) plus BV, 21 patients received capecitabine and OX plus BV, 10 patients received S-1 and OX plus BV and 7 patients received FOLFOX plus cetuximab or panitumumab. The median PFS was 11.5 months (95% confidence interval [CI] 8.3–16.0), the median OS was 45.4 months (95% CI 37.4–NA), and the RR was 56.0% (95% CI 42.3–68.8). Adverse events of grade ≥ 3 that occurred in ≥ 5% of cases were neutropenia in 6 patients (12%), peripheral sensory neuropathy in 5 patients (10%), diarrhea in 4 patients (8%), hypertension in 4 patients (8%), anorexia in 3 patients (6%) and allergic reactions in 3 patients (6%).

Conclusions First-line chemotherapy with re-introduction of OX more than 6 months after adjuvant chemotherapy including OX can be used safely with expected efficacy for relapsed colon cancer patients.

Keywords Oxaliplatin · Re-introduction · Colon cancer
Introduction

Colon cancer is the third-most commonly diagnosed cancer, with an estimated 1,400,000 new cases and 700,000 deaths globally each year [1]. Chemotherapy is an essential method of colon cancer treatment [2–4]. Among the various chemotherapy agents, oxaliplatin (OX) is one of the most substantial key agents for colon cancer treatment in both adjuvant and unresectable-metastatic disease settings.

Thus far, three pivotal studies have shown that OX-based adjuvant chemotherapy, such as infusional 5-fluorouracil, l-leucovorin and OX (FOLFOX) or capecitabine and OX (CAPOX), for colon cancer significantly improved both the overall survival (OS) and disease-free survival [5–7]. OX-based adjuvant chemotherapy for colon cancer has been widely accepted and performed in clinical practice, and FOLFOX and CAPOX are also widely used in both the first and the second lines for metastatic colon cancer [8–10]. However, there is little supporting evidence available, and few studies have evaluated the efficacy and safety of OX re-introduction as the first-line treatment for relapsed colon cancer after OX-based adjuvant chemotherapy [11, 12]. To establish the optimal use of OX for colon cancer treatment, it is necessary to investigate the clinical benefit of OX re-introduction as the first-line treatment for relapsed disease after OX-based adjuvant chemotherapy.

The present study evaluated the efficacy and safety of first-line chemotherapy with re-introduction of OX more than 6 months after the completion of adjuvant chemotherapy with an OX-containing regimen.

Patients and methods

Study design

This study was a single-arm, multicenter, phase II study to evaluate the efficacy and safety of physician’s choice OX-based regimen for colon cancer patients with neuropathies of grade < 1 who relapsed more than 6 months after OX-based adjuvant chemotherapy.

Study data and informed consent were obtained in accordance with the Declaration of Helsinki. The Certified Clinical Research Review Board of Aichi Medical University Hospital approved this study protocol. This trial was registered with the UMIN Clinical Trials Registry as UMIN 000011348 https://upload.umin.ac.jp/cgi-open-bin/ctr/ctr_view.cgi?recptno=R000013300. This trial was registered with the Japan Registry of Clinical Trials as jRCTs041180118; all patients were given a written explanation and provided their written informed consent before participating.

Inclusion and exclusion criteria

Tumors were staged according to the UICC version 7 [13]. The inclusion criteria were as follows: (1) stage II/III colon cancer with neuropathies of grade ≤ 1 who relapsed more than 6 months after adjuvant chemotherapy including OX; (2) performance status of 0–1; (3) ≥ 20 years of age; (4) presence of at least one measurable lesion using the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1; (5) past history of adjuvant chemotherapy including OX with a cumulative dose of more than 300 mg/m²; (6) adequate hematologic, liver, and coagulation profiles and normal electrocardiogram findings; and (7) consent given to participate in this clinical study. The exclusion criteria were as follows: (1) serious coexisting morbidities; (2) active synchronous or metachronous malignant disease; (3) pregnant or lactating; (4) not considered suitable for participation for any other reason.

Treatment methods

Eligible patients were treated with infusional FOLFOX plus molecularly targeted agents or CAPOX plus bevacizumab (BV) or S-1 and OX (SOX) plus BV. Selection of OX-based regimen was decided by the attending physician at registration of each patient. FOLFOX was administered as a 2-h OX 85 mg/m² infusion on day 1 in tandem with a 2-h l-leucovorin 200 mg/m² infusion on day 1 and 5-FU as a 400-mg/m² bolus followed by a 46-h 2400 mg/m² infusion on days 1 to 3, every 2 weeks. In addition, BV (5 mg/kg on day 1) or cetuximab (400 mg/m² as the initial dose and 250 mg/m² as the subsequent doses on days 1 and 8) or panitumumab (6 mg/kg on day 1) was combined with FOLFOX. CAPOX plus BV was administered as intravenous OX 130 mg/m² on day 1, oral capecitabine 1000 mg/m² twice daily from the evening of day 1 to the morning of day 15 and BV 7.5 mg/kg on day 1, every 3 weeks. SOX plus BV was administered as intravenous OX 130 mg/m² on day 1, oral S-1 40 mg/m² twice daily from the evening of day 1 to the morning of day 15 and BV 7.5 mg/kg on day 1, every 3 weeks.

Endpoints

The primary endpoint was the progression-free survival (PFS). The secondary endpoints were the OS, response rate (RR) and the safety of the combination therapy. Radiographic image studies were performed every eight weeks. The RR was evaluated by the RECIST 1.1 criteria [14]. All adverse events recorded were graded according to the Common Terminology Criteria for Adverse Events of the National Cancer Institute (CTCAE) version 4.0 [15]. The PFS was defined as the period between the day of...
registration and progression or death, whichever came first. Patients were censored at the last point when no progress-
ion was confirmed if the patients did not experience any event associated with the PFS. The OS was defined as the period between the day of registration and death. The data of patients who had not experienced an event were censored at the date of the final observation.

**Statistical analyses**

We set the threshold median PFS at 7 months and the expected median PFS at 10.5 months based on the results of a previous study [16–19]. Given a 2-sided alpha of 0.05 and statistical power of 80% with about 10% ineligible or dropout patients, we set 50 patients as the target sample size in this study.

The analytical population for efficacy was defined as all eligible patients, and that of safety was defined as all eligible patients who received treatment at least once. In the present study, disease control rate (DCR) was defined as the percentage of complete response, partial response, and stable disease in full set analysis. The PFS and OS curves were calculated using the Kaplan–Meier method, and the 95% confidence interval (CI) was estimated using the Brookmeyer and Crowley method with log–log transformation. All analyses were implemented by SAS 9.4, SAS/STAT 14.2 (SAS Institute, Cary, NC, USA).

**Results**

**Patients’ background characteristics**

From September 2013 to May 2019, 50 patients were reg-
istered from 21 institutions. The intention-to-treat analysis and safety analysis were carried out on those 50 patients.

Table 1 shows the patients’ background characteristics. Twenty-eight patients were male, and 22 were female, with a median age of 69.5 years (range 27–82 years). The time until recurrence from the completion of adjuvant therapy was 6–12 months in 16 patients, 12–24 months in 15 patients and more than 24 months in 19 patients. The median total dose of OX for adjuvant chemotherapy were 1136 (470–1904) mg/body. The most common metastatic site was the lung (22 patients, 44%), lymph node (19 patients, 38%), peritoneal metastasis (13 patients, 26%) and liver (11 patients, 22%). The median follow-up was 34.3 months (range 20.8–63.7 months). Twelve patients received FOL-
FOX plus BV, 21 patients received CAPOX plus BV, 10 patients received SOX plus BV, and 7 patients received FOLFOX plus cetuximab or panitumumab.

| Table 1 Patient characteristics | No. of patients | (%) |
|---------------------------------|----------------|-----|
| **Gender**                      |                |     |
| Male                            | 28             | 56.0|
| Female                          | 22             | 44.0|
| **Age (years)**                 |                |     |
| Median                          | 69.5           |     |
| Range                           | 27–82          |     |
| **Performance status (PS)**     |                |     |
| 0                               | 44             | 88.0|
| 1                               | 6              | 12.0|
| **Cancer location**             |                |     |
| Colon                           | 29             | 58.0|
| Rectum                          | 21             | 42.0|
| **Previous adjuvant chemotherapy** |            |     |
| FOLFOX                          | 16             | 32.0|
| CAPOX                           | 32             | 64.0|
| Other                           | 2              | 4.0 |
| **Time from adjuvant chemotherapy** |            |     |
| 6–12 months                     | 16             | 32.0|
| 12–24 months                    | 15             | 30.0|
| More than 24 months             | 19             | 38.0|
| **Oxaliplatin free interval**   |                |     |
| 6–12 months                     | 15             | 30.0|
| 12–24 months                    | 14             | 28.0|
| More than 24 months             | 21             | 42.0|
| **Baseline peripheral sensory neuropathy** | | |
| 0                               | 31             | 62.0|
| 1                               | 19             | 38.0|
| **Number of relapse site**      |                |     |
| 0                               | 0              | 0   |
| 1                               | 32             | 64.0|
| ≥2                              | 18             | 36.0|

**FOLFOX** infusional 5-fluorouracil, l-leucovorin and oxaliplatin, **CAPOX** capcitabine and oxaliplatin, Intention to treat population, n = 50

**Efficacy**

All follow-up data were collected by Dec/2019 and the median follow-up period was 34.3 months. The median PFS was 11.5 months (95% CI 8.3–16.0 months) (Fig. 1). The median PFS among subgroups based on time from the completion of adjuvant chemotherapy (6–12 months/12–24 months/more than 24 months) was comparable [13.0 months (95% CI 7.0–19.2)/11.0 months (95% CI 7.5–19.9)/12.7 months (95% CI 7.8–17.7), respectively]. The median OS was 45.4 months (95% CI 37.4 months–NA) (Fig. 2). The reasons for discontinuing the study treatment included progression of the primary disease in 26 patients (54.2%), adverse events in 5 patients (10.4%)
(Platelet count decreased was 2 patients, Urine protein was 1 patient, Neutropenia was 1 patient, Anorexia was 1 patient), discretion of the physician in 4 patients (8.3%), refusal by 6 patients (12.5%) and withdrawal of 3 patients (6.3%) due to confirmation of complete response (CR). Two patients continued the protocol treatment. The median OS among subgroups based on time from the completion of adjuvant chemotherapy (6–12 months/12–24 months/more than 24 months) was comparable [44.6 months (95% CI, 24.6-NA)/45.4 months (95% CI, 27.3-NA)/61.3 months (95% CI, 18.6-NA), respectively]. According to the subgroup analysis for OX-free interval, the median PFS and OS were 13.4 months (95% CI 7.0–19.2) and NA months (95% CI 41.9–NA) respectively for 6–12 months, 10.4 months (95% CI 7.4–19.9) and 37.4 months (95% CI 18.7–NA) respectively for 12–24 months, and 12.1 months (95% CI 7.7–17.5) and 45.4 months (95% CI 29.8–NA) respectively for more than 24 months.

Table 2 shows the efficacy data. The best overall RR was 56.0% (95% CI 42.3–68.8%). The disease control rate (DCR) was 86.0% (95% CI 73.5–93.4%). In the present study, the best overall RR for OX-free interval was 53.3% (8/15) for
Table 2 Efficacy data

| Parameter                        | Number of patients | (%)     |
|----------------------------------|--------------------|---------|
| Best overall response rate       | 5                  | 10.0    |
| Complete response (CR)           | 23                 | 46.0    |
| Partial response (PR)            | 15                 | 30.0    |
| Stable disease (SD)              | 4                  | 8.0     |
| Progressive disease (PD)         | 3                  | 6.0     |
| Best overall response rate (CR + PR) | 28 | 56.0    |
| 95% CI                           | 43                 | 86.0    |
| Disease control rate (CR + PR + SD) | 43 | 73.5–93.4 |

There was no case of grade 4 adverse event or treatment-related death.

Table 3 shows the treatment exposure. The median total dose of OX was 525 mg/m² (85–1690 mg/m²). The median total dose of OX was 348 mg/m² (85–1615 mg/m²) for FOLFOX plus BV, 650 mg/m² (130–1645 mg/m²) for CAPOX plus BV, 525 mg/m² (260–1690 mg/m²) for SOX plus BV and 770 mg/m² (170–1235 mg/m²) for FOLFOX plus cetuximab or panitumumab. The median course of the study treatment was 14 cycles in FOLFOX plus BV, 10 cycles in CAPOX plus BV, 6 cycles in SOX plus BV and 15 cycles in FOLFOX plus cetuximab or panitumumab.

Adverse events (AEs) of any grade were observed in 88.0% (44/50 patients) of patients. Table 4 shows the details of the AEs. Adverse events of grade 3 that occurred in ≥ 5% of cases were neutropenia in 6 patients (12%), peripheral sensory neuropathy in 5 patients (10%), diarrhea in 4 patients (8%), hypertension in 4 patients (8%), anorexia in 3 patients (6%) and allergic reactions in 3 patients (6%). There was no case of grade 4 adverse event or treatment-related death.

Discussion

The present study evaluated the efficacy and safety of first-line chemotherapy with re-introduction of OX more than six months after the completion of adjuvant chemotherapy including OX. Our findings suggested that first-line chemotherapy with re-introduction of OX more than 6 months after adjuvant chemotherapy including OX could be used safely with the expected efficacy for relapsed colon cancer patients. Therefore, the re-introduction of OX treatment is a viable option for relapsed colon cancer patients who have already been treated with OX-based adjuvant chemotherapy.

The present study showed that the median PFS was 11.5 months for first-line chemotherapy with re-introduction of OX after adjuvant chemotherapy including OX for colon cancer. In the adjuvant setting, very recently, Kotaka et al. showed the similar results. They evaluate the efficacy of reintroducing FOLFOX or CAPOX with or without BV in relapsed 31 colorectal cancer patient who treated OX as adjuvant chemotherapy between October 2012 and October 2016 [12]. They found that median PFS was 10.8 months (95% CI 6.9–18.8 months). In a metastatic setting, recently, a few studies have evaluated the clinical effects of the re-introduction of OX for colorectal cancer after chemotherapy including OX. de Gramont et al. performed an additional analysis of the OPTIMisation of OXaliplatin (OPTIMOX) trial to evaluate the efficacy of OX re-introduction for metastatic colorectal cancer patients. They found that OX re-introduction had an independent and significant impact on the OS (hazard ratio: 0.56, \( P = 0.009 \)) [20]. In addition, Chibaudel et al. evaluated the clinical effects of the re-introduction of OX-based chemotherapy and the OX-free interval (OFI; cut-off value: 6 months) on tumor sensitivity to OX re-introduction in initially unresectable colorectal cancer who received first-line OX-based chemotherapy.
The PFS and OS were 3.0 and 8.8 months in patients with an OFI < 6 months, respectively, and 5.5 and 16.8 months in patients with an OFI ≥ 6 months, respectively. Furthermore, an OFI of ≥ 6 months improved the survival. Given these results, even after chemotherapy including OX, the re-introduction of OX might improve the survival among colon cancer patients, according to the OFI.

In the present study, the best overall RR and DCR were 56.0% and 86.0%, respectively. Although the patient background characteristics and treatment lines have differed among studies, there have been some showing OX sensitivity in patients after OX-based chemotherapy in both adjuvant and metastatic setting. Table 5 summarized the efficacy of the present study and previous studies. In adjuvant setting, Kotaka et al. reported that the RR was 62.1% (95% CI 42.3–79.3) and the DCR was 82.8% (95% CI 64.2–94.2). The RR for oxaliplatin-free interval was 100.0% in months 6–12 and 56.0% after 12 months. In metastatic setting, Suenaga et al. evaluated the re-introduction of OX-based chemotherapy in 33 metastatic colorectal cancer refractory to standard treatment [24]. They reported that the RR was 6.1% (95% CI 2.5–14.7%) and the DCR 66.7% (95% CI 49.7–83.6%). Goebel et al. investigated FOLFOX re-introduction after a break in treatment or following disease progression on another regimen in 29 cases of metastatic colorectal cancer. They found that the re-introduction of OX was feasible and achieved a response or stabilization in 73% of patients [21]. In addition, the OPTIMOX-1 and OPTIMOX-2 studies showed an RR of 19% and DCR of 58%. Interestingly, the OPTIMOX-1 and OPTIMOX-2 studies also showed that the tumor sensitivity differed between the patients with an OFI < 6 months and ≥ 6 months. The respective DCR and RR were 14% and 45% in those with an OFI < 6 months and 22% and 63% in those with an OFI ≥ 6 months. In addition, the progression disease rate sharply decreased from 52% in the patients with an OFI < 6 months to 23% in those with an OFI ≥ 6 months. Although it is difficult to directly compare the results due to differences in the patient profiles and treatments, even after OX-based chemotherapy, the patients still have a potentially OX-sensitive tumor. Furthermore, the tumor sensitivity might also change depending on the OFI.

The present study showed that AEs of any grade were observed in 88% of patients. The incidence of both peripheral sensory and motor neuropathies were not increased. According to previous reports, the incidence of the AEs was acceptable. On other hands, in the previous similar reports, the rate of grade 1/2 and 3 allergic reaction was 12.9% and 3.2%, respectively [12]. The rate of grade 1/2 and 3 allergic reaction of the present study was higher than

| Table 4 | Relevant adverse events occurring in ≥ 10% of patients (highest grade per patients) |
| Adverse event | Grade 3/4 | All Grade |
| | Number of patients (%) | Number of patients (%) |
| Hematological | | |
| Leukopenia | 0 0 | 25 50.0 |
| Neutropenia | 6 12.0 | 26 52.0 |
| Anemia | 0 0 | 26 52.0 |
| Thrombocytopenia | 0 0 | 28 56.0 |
| No hematological | | |
| ALP increased | 1 2.0 | 20 40.0 |
| Blood bilirubin increased | 0 0 | 21 42.0 |
| Creatine increased | 0 0 | 11 22.0 |
| Peripheral sensory neuropathy | 5 10.0 | 45 90.0 |
| Peripheral motor neuropathy | 2 4.0 | 17 34.0 |
| Stomatitis | 1 2.0 | 24 48.0 |
| Nausea | 2 4.0 | 29 58.0 |
| Vomiting | 1 2.0 | 10 20.0 |
| Diarrhea | 4 8.0 | 20 40.0 |
| Rash | 1 2.0 | 20 40.0 |
| Paronychia | 1 2.0 | 8 16.0 |
| Anorexia | 3 6.0 | 36 72.0 |
| Fatigue | 0 0 | 35 70.0 |
| Allergic reaction | 3 6.0 | 11 22.0 |
| Hand foot syndrome | 0 0 | 27 54.0 |
| Hypertension | 4 8.0 | 18 36.0 |
| Hemorrhage | 0 0 | 8 16.0 |

Table 5 | Summary of the efficacy of the present study and previous studies |
| Study population setting | Present study | REACT study [Ref. 12] | RE-OPEN study [Ref. 24] | Goebel et al. [Ref. 21] |
| Study population setting | OX-based adjuvant chemotherapy | OX-based adjuvant chemotherapy | OX-based chemotherapy for metastatic setting | OX-based chemotherapy for metastatic setting |
| Sample size | 50 patients | 31 patients | 33 patients | 29 patients |
| Progression free survival | 11.5 months | 10.8 months | 98 days | 18 weeks |
| Overall survival | 45.4 months | 28.7 months | 300 days | 42 weeks |
| Response rate | 56.0% | 62.1% | 6.1% | 21% |
| Disease control rate | 86.0% | 82.8% | 39.4% | 73% |
in the previous study. However, the allergic reaction was not main reason for discontinuation of treatment. Therefore, first-line chemotherapy with re-introduction of OX more than 6 months after adjuvant chemotherapy including OX seems able to be used safely for relapsed colorectal cancer patients.

Several limitations associated with the present study warrant mention. First, there might have been some selection bias. This study was a single-arm, multicenter, phase II study and thus might only have included patients considered suited for OX-based chemotherapy. Second, the optimal OFI was unclear. In the present study, we set the OFI as 6 months according to previous studies. It is unclear whether or not a longer OFI affects the survival and OX sensitivity. However, this issue is a difficult problem to solve, because the early relapse after adjuvant chemotherapy is related to more aggressive tumor. Third, we did not collect the proportion against the expected dose of OX in the adjuvant chemotherapy. Although the median dose of the OX in the present study was similar to previous study; the proportion against the expected dose of OX in the adjuvant chemotherapy was important information for sensitivity in OX re-introduction as the first-line treatment after OX-based adjuvant chemotherapy. Considering these, the further study will clarify these issues.

In conclusion, first-line chemotherapy with re-introduction of OX more than 6 months after completion of adjuvant chemotherapy that had included OX was able to be used safely with the expected efficacy for relapsed colon cancer patients. The re-introduction of OX treatment appears to be a viable treatment option for relapsed colon cancer patients treated with OX-based adjuvant chemotherapy.

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Compliance with ethical standards

Conflict of interest Hironaga Satake has received research funding from Ono Pharmaceutical Co. Ltd., Taiho Pharmaceutical Co. Ltd., Takeda Pharmaceutical Co., Ltd., Daiichi Sankyo Co., Ltd., Sanofi Co., Ltd., and honoraria from Bayer Co., Ltd., Bristol-Myers Squibb Co., Ltd., Chugai Pharmaceutical Co., Ltd., Daiichi Sankyo Co., Ltd., Eli Lilly Japan Co., Ltd., Merck Bio Pharma Co., Ltd., MSD Co., Ltd., Ono Pharmaceutical Co., Ltd., Sanofi Co., Ltd., Taiho Pharmaceutical Co., Ltd., Takeda Co., Ltd. and Yakult Honsha Co., Ltd.

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References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A (2018) Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 68(6):394–424
2. Glimelius B, Tietj E, Cervantes A, Arnold D, ESMO Guidelines Working Group (2013) Rectal cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 24(Suppl 6):vi81–vi88
3. Van Cutsem E, Nordlinger B, Cervantes A, ESMO Guidelines Working Group (2010) Advanced colorectal cancer: ESMO Clinical Practice Guidelines for treatment. Ann Oncol 21(Suppl 5):v93–v97
4. Cunningham D, Atkin W, Lenz HJ, Lynch HT, Minsky B, Nordlinger B, Starling N (2010) Colorectal cancer. Lancet 375(9719):1030–1047
5. André T, Boni C, Mouriedj-Boudiaf L, Navarro M, Taberner N, Hickish T, Topham C, Zaninelli M, Clinha P, Bridgewater J, Tabah-Fisch I, De Gramont A, Multicenter International Study of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer (MOSAIC) Investigators (2004) Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. N Engl J Med 350(23):2343–2351
6. Kuebler JP, Wiaend HS, O’Connell MJ, Smith RE, Colangelo LH, Yohlers G, Petrelli NJ, Findlay MP, Seay TE, Atkins JN, Zapas JL, Goodwin JW, Fehrenbacher L, Ramanathan HK, Conley BA, Flynn PJ, Soori G, Colman LK, Levine EA, Lanier KS, Wolmark N (2007) 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 25(16):2195–2204
7. Haller DG, Taberner J, Maroun J, de Braud F, Price T, Van Cutsem E, Hill M, Gilberg F, Rittweger K, Schmoll HJ (2011) Capecitabine plus oxaliplatin compared with fluorouracil and folinic acid as adjuvant therapy for stage III colorectal cancer. J Clin Oncol 29(11):1465–1471
8. Cassidy J, Clarke S, Díaz-Rubio E, Scheithauer W, Figer A, Wong R, Koski S, Lichinets M, Yang TS, Rivera F, Couture F, Sirzén F, Saltz L (2008) Randomized phase III study of capecitabine plus oxaliplatin compared with fluorouracil/folinic acid plus oxaliplatin as first-line therapy for metastatic colorectal cancer. J Clin Oncol 26(12):2006–2012
9. Cassidy J, Clarke S, Díaz-Rubio E, Scheithauer W, Figer A, Wong R, Koski S, Rittweger K, Gilberg F, Saltz L (2011) XELOX vs FOLFOX-4 as first-line therapy for metastatic colorectal cancer: NO16966 updated results. Br J Cancer 105(1):58–64
10. Rothenberg ML, Cox JV, Butts C, Navarro M, Bang YJ, Goel R, Gollins S, Siu LL, Laguerre S, Cunningham D (2008) Capecitabine plus oxaliplatin (XELOX) versus 5-fluorouracil/folinic acid plus oxaliplatin (FOLFOX-4) as second-line therapy in metastatic colorectal cancer.}

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colorectal cancer: a randomized phase III noninferiority study. Ann Oncol 19(10):1720–1726
11. Schmoll HJ, Twelves C, Sun W, O’Connell MJ, Cartwright T, McKenna E, Saif M, Lee S, Youthers G, Haller D (2014) Effect of adjuvant capecitabine or fluorouracil, with or without oxaliplatin, on survival outcomes in stage III colon cancer and the effect of oxaliplatin on post-relapse survival: a pooled analysis of individual patient data from four randomised controlled trials. Lancet Oncol 15(13):1481–1492
12. Kotaka M, Iwamoto S, Satake H, Sakai D, Kudo T, Fukunaga M, Konishi K, Ide Y, Ikumoto T, Tsuji A, Sano Y, Kato T, Sugimoto N, Sato H, Kanazawa A, Kurata T, Yamanaka T, Tomita N (2020) Evaluation of FOLFOX or CAPOX reintroduction with or without bevacizumab in relapsed colorectal cancer patients treated with oxaliplatin as adjuvant chemotherapy (REACT study). Int J Clin Oncol. https://doi.org/10.1007/s10147-020-01701-1 (PMID: 32409917)
13. Sobin LH, Gospodarowicz MK, Wittekind Ch (eds) (2009) International Union Against Cancer (UICC) TNM classification of malignant tumors, 7th edn. Wiley, Oxford
14. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent DM, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D, Verweij J (2009) New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 45(2):228–247
15. Common Terminology Criteria for Adverse Events v4.0 (CTCAE). https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/Archive/CTCAE_4.0_2009-05-29_QuickReference_8.5x11.pdf. Accessed 28 May 2009
16. de Gramont A, Chibaudel LB, Bourges O, Perez-Staub N, Tournigand C, MAindraut-Goebel F, André T, Larsen AK, Afchain P, Louvet C (2009) Definition of oxaliplatin sensitivity in patients with advanced colorectal cancer previously treated with oxaliplatin-alone therapy. J Clin Oncol 27(15 suppl):4024
17. Yamazaki K, Nagase M, Tamagawa H, Ueda S, Tamura T, Murata K, Eguchi Nakajima T, Baba E, Tsudo M, Moriwaki T, Tsuji Y, Tsuji Y, Muro K, Taira K, Denda T, Funai S, Shinozaki K, Yamashita H, Sugimoto N, Okuno T, Nishina T, Uemki M, Kurihito T, Takayama T, Tsuji A, Yoshida M, Hosokawa A, Shibata Y, Suyama K, Okabe M, Suzuki K, Seki N, Kawakami K, Sato M, Fujikawa K, Hirashima T, Shimura T, Taku K, Otsuji T, Tamura F, Shinozaki E, Nakashima K, Hara H, Tsushima T, Ando M, Morita S, Boku N, Hyodo I (2016) Randomized phase III study of bevacizumab plus FOLFIRI and bevacizumab plus mFOLFOX6 as first-line treatment for patients with metastatic colorectal cancer (WJOG4407G). Ann Oncol 27(8):1539–1546. https://doi.org/10.1093/annonc/mdw206
18. Saltz LB, Clarke S, Diaz-Rubio E, Scheithauer W, Figer A, Wong R, Koski S, Lichinitser M, Yang TS, Rivera F, Couture F, Siržén F, Cassidy J (2008) Bevacizumab in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer: a randomized phase III study. J Clin Oncol 26(12):2013–2019. https://doi.org/10.1200/JCO.2007.14.9930
19. de Gramont A, Buyse M, Abrahantes JC, Burzykowski T, Quinaux E, Cervantes A, Figer A, Lledo G, Flesch M, Mineur L, Carola E, Etienne PL, Rivera F, Chirivella I, Perez-Staub N, Louvet C, André T, Tabah-Fisch I, Tournigand C (2007) Reintroduction of oxaliplatin is associated with improved survival in advanced colorectal cancer. J Clin Oncol 25(22):3224–3229
20. Maïndraut-Goebel F, Tournigand C, André T, Carola E, Mabro M, Artru P, Louvet C, de Gramont A (2004) Oxaliplatin reintroduction in patients previously treated with leucovorin, fluorouracil and oxaliplatin for metastatic colorectal cancer. Ann Oncol 15(8):1210–1214
21. Chibaudel B, Maïndraut-Goebel F, Lledo G, Mineur L, André T, Bennamoun M, Mabro M, Artru P, Carola E, Flesch M, Dupuis O, Colin P, Larsen AK, Afchain P, Tournigand C, Louvet C, de Gramont A (2009) Can chemotherapy be discontinued in unrespectable metastatic colorectal cancer? The GERCOR OPTIMOX2 Study. J Clin Oncol 27(34):5727–5733
22. Tournigand C, Cervantes A, Figer A, Lledo G, Flesch M, Buyse M, Mineur L, Carola E, Etienne PL, Rivera F, Chirivella I, Perez-Staub N, Louvet C, André T, Tabah-Fisch I, de Gramont A (2006) OPTIMOX1: a randomized study of FOLFIRI or FOLFOX7 with oxaliplatin in a stop-and-Go fashion in advanced colorectal cancer—a GERCOR study. J Clin Oncol 24(3):394–400
23. Suenaga M, Mizunuma N, Matsusaka S, Shinozaki E, Ozaka M, Ogura M, Yamaguchi T (2015) Phase II study of oxaliplatin plus bevacizumab for advanced colorectal cancer in patients previously treated with oxaliplatin and irinotecan: RE-OPEN study. Drug Des Dev Ther 9:3099–3108

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