International Journal of Clinical Oncology (2019) 24:836–841
https://doi.org/10.1007/s10147-019-01414-0

ORIGINAL ARTICLE

Biweekly S-1 plus oxaliplatin (SOX) reintroduction in previously treated metastatic colorectal cancer patients (ORION 2 study): a phase II study to evaluate the efficacy and safety

Hiroaki Tanioka[1] · Michitaka Honda[2] · Chihiro Tanaka[3] · Yoshitaka Morita[4] · Keiichiro Ishibashi[5] · Takeshi Kato[6] · Chu Matsuda[7] · Masato Kataoka[8] · Hironaga Satake[9] · Yoshinori Munemoto[10] · Kenji Kobayashi[11] · Masazumi Takahashi[12] · Ken Nakata[13] · Junichi Sakamoto[14] · Koji Oba[15] · Hideyuki Mishima[16]

Received: 1 November 2018 / Accepted: 6 February 2019 / Published online: 18 February 2019

Abstract

Background The reintroduction of oxaliplatin as a third-or-later-line regimen has been a promising option for patients with metastatic colorectal cancer (mCRC) who previously received chemotherapy including oxaliplatin. In this single-arm phase II study, we evaluated the efficacy of biweekly SOX, which is the combination of oxaliplatin reintroduction and S-1, as a third-or-later-line treatment.

Methods Patients with mCRC who had previously received prior chemotherapy including oxaliplatin and irinotecan and were planned to receive the reintroduction of oxaliplatin were enrolled. Oxaliplatin (85 mg/m^2) with/without bevacizumab (5 mg/kg) was given intravenously on day 1. Oral S-1 was administered on day 2–8 at a dose of 40–60 mg (calculated according to the body surface area) twice a day. Cycles were repeated every 2 weeks. The primary endpoint was the progression-free survival (PFS); our hypothesis was that the median PFS would be 3.5 months with a minimum threshold above 2.0 months. The secondary endpoints included the adverse events (AEs), response rate and overall survival (OS).

Results A total of 41 patients from 12 institutes were enrolled. The median PFS and OS survival were 3.3 months (95% confidence interval [CI] 2.7–4.2) and 10.1 months (8.3–14.6), and response rate and disease control rate were 10.0% and 65.0%, respectively. Grade 3 AEs included thrombocytopenia (5.0%), anorexia (5.0%), pneumonia (5.0%) and fatigue (5.0%). There were no cases of grade 4 AEs or treatment-related death.

Conclusion Biweekly SOX regimen with reintroduction of oxaliplatin could be exploitable as the third- and/or later-line treatments for patients with mCRC.

Keywords Metastaic colorectal cancer · Oxaliplatin reintroduction · Biweekly SOX

Introduction

The development of molecular-targeted drugs has been progressing recently all around the world, providing clinicians with several options now in the treatment of colorectal cancer (CRC) [1]. By considering the gene mutation profile or site of the primary lesion in each patient, we can choose the ideal regimen of molecular-targeted drugs [1–4]. Regarding cytotoxic doublets, the combination of 5-FU, irinotecan and oxaliplatin remains the standard drug regimen, and one of the goals of treatment for metastatic colorectal cancer (mCRC) is to administer all of these key drugs while maintaining a good general condition for the patient [5].

While oxaliplatin-induced sensory neuropathy remains a clinical issue for patients, a clinical trial has shown that the incidence of grade 2 and 3 neurotoxicity increases along with the number of cycles, being 10% after 9 cycles, 25% after 12 cycles and 50% after 14 cycles using a dose of 85 mg/m^2 per cycle [6]. Since oxaliplatin-related neurotoxicity is reversible in the early phase, the reintroduction of oxaliplatin after failure of a second-line regimen has been considered a promising strategy in such cases [7–9]. After treatment using irinotecan-based regimens, the

The second author Michitaka Honda has equally contributed to this study as the first author, i.e., Hiroaki Tanioka.

✉ Michitaka Honda
mhonda@fukushimamed.com

Extended author information available on the last page of the article

reintroduction of oxaliplatin-based doublets, such as FOLFOX or XELOX, has been accepted as the preferred "stop and go" treatment protocol for mCRC [8]. However, neuropathy remains the major dose-limiting toxicity. We previously conducted the ORION study [17] to investigate the effectiveness of biweekly XELOX in the third or later line for mCRC. This biweekly XELOX regimen includes 85 mg/m^2 oxaliplatin—two-thirds of the triweekly regimen, which includes 130 mg/m^2 on day 1, could be reducing the neurotoxicity in the reintroduction phase. Indeed, the incidence of grade 3 or 4 peripheral neuropathy with this biweekly regimen was lower than that with the standard triweekly regimen: 9.1% versus 0%, respectively. Although the survival benefit of biweekly XELOX was not shown, our findings suggested that the regimen might be able to prevent neurotoxicity.

We newly conducted the present Phase II study followed by the ORION study to evaluate the survival outcomes of biweekly oxaliplatin plus S-1 (SOX) as the reintroduction regimen of oxaliplatin for mCRC. S-1, an oral prodrug of 5-FU, is a common option for treating CRC patients in Asian countries, and some previous reports have shown the oncological noninferiority of a regimen replacing the continuous infusion of 5-FU or capecitabine with that of S-1 in mCRC patients [10–14]. In addition, recent reports have also described the outcomes of biweekly SOX for CRC [15, 16]. Confirming the efficacy of biweekly SOX in such a situation would be extremely clinically relevant for physicians treating mCRC patients, and we expect that our findings will prove helpful to this end.

Patients and methods

Study design

The present study was a multicenter and single-arm phase II trial performed at 12 Japanese institutions (http://www.umin.ac.jp/: UMIN 000013277). The trial was conducted in accordance with the Declaration of Helsinki and all of the applicable local laws and regulations. Approval for the protocol was obtained from the institutional review boards of all of the participating hospitals.

Participants

All of the patients submitted their written informed consent form before the initiation of the trial treatment. The eligible and exclusion criteria were the same as in our previous study [17]. In brief, patients who had histologically confirmed mCRC, measurable lesions and a history of chemotherapy including oxaliplatin and irinotecan with more than 'stable disease' effectiveness were eligible for the study. Patients were scheduled to receive reintroduction of oxaliplatin as a third-or-later-line regimen once at least 6 months had passed since the last administration of oxaliplatin. The other eligibility criteria included age over 20 years old, an Eastern Cooperative Oncology Group performance status (ECOG-PS) score of 0–2 and adequate hematological, renal, and hepatic functions. The exclusion criteria were the presence of severe peripheral neuropathy, other malignant tumors or brain metastases, uncontrolled ascites, diathesis or bowel obstruction, clinically significant cardiovascular disease, pulmonary disease, cerebral diseases, metabolic disorder, bleeding disorder, serum positivity for hepatitis virus antigen and an active infection or psychiatric conditions.

Study treatment

The patients received oxaliplatin (85 mg/m^2) with/without bevacizumab (5 mg/kg) were given intravenously on day 1 and S-1 (40–60 mg) twice daily on days 2–8 every other day. This trial regimen was repeatedly performed every 2 weeks. In the case of failure of oxaliplatin due to severe adverse events, the trial treatment was converted to S-1 with/without bevacizumab. The dose of S-1 was adjusted according to the body surface area (BSA) of the individuals as follows: 80, 100 or 120 mg per day for BSA < 1.25 m^2, 1.25–1.50 m^2 and BSA ≥ 1.50 m^2, respectively. Other dose modifications (as specified in the study protocol) were permitted based on the patient's renal function or in the event of treatment-related toxicity. The alternative-day administration of S-1 was also permitted.

Outcomes

The primary endpoint was progression-free survival (PFS). The secondary endpoints included the overall survival (OS), time to treatment failure (TTF), response rate and disease control rate of measurable lesions defined by the Response Evaluation Criteria in Solid Tumors (RECIST) vesion1.1 criteria [18] as well as the relative dose intensity (RDI) and other AEs. The size of lesions was measured by computed tomography or magnetic resonance imaging at baseline. The target lesions were evaluated by investigators in accordance with the RECIST version 1.1 criteria. Laboratory evaluations were performed before treatment or on day 15. AEs were assessed according to the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0. The causality relationship between the study regimen and any given AE was assessed by the investigator. All AEs occurring up to 28 days after the final dose of the studied medication were reported.

Statistical analyses

The estimated PFS of third-or-later-line treatment for mCRC ranged from 8 weeks to 2.0 months in previous trials conducted to investigate the efficacy of molecular-targeted therapy [19–21]. The "Re-open study", which was conducted to evaluate the efficacy of oxaliplatin reintroduction as a third-or-later-line regimen for mCRC, showed a PFS of 98 days [22]. Considering these previous results, we estimated the median PFS of this trial regimen of "biweekly SOX" to be 3.5 months with a lower threshold of 2.0 months. As a result, we calculated the necessary sample size for a two-sided alpha of 0.05 and statistical power of 90%, including some drop-out cases, to be 40 patients. Other time-to-event values (TTF, PFS and OS) were assessed using the Kaplan–Meier method, and the median value of each endpoint was estimated with 95% confidence intervals (CIs) using the method of Brookmeyer and Crowley. All analyses were conducted using the SAS software program, ver. 9.4. (SAS Institute Inc., Cary, NC, USA).

Results

Patients' characteristics

From June 2014 to April 2016, a total of 41 patients from 12 hospitals were registered in the trial and were included in the intention-to-treat population. Since one patient withdrew consent, 40 patients were inclued in the safty evaluation (Fig. 1). The demographic and baseline characteristics of the patients are shown in Table 1. All patients were treated with oxaliplatin-based regimen in first line except two cases who received FORFIRI as a first-line treatment. All of the follow-up data were collected by April 2017. The median-treated course was 5 (0–24); one patient declined to participate in this study. The median follow-up period was 27.6 months.

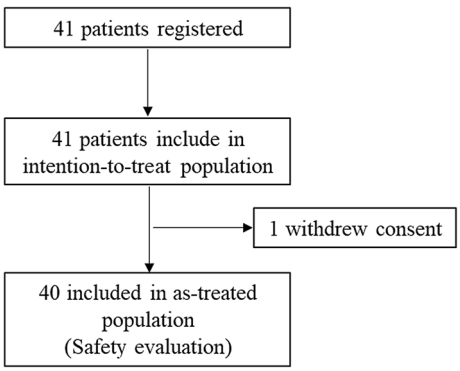

Fig. 1 Patients flow

Table 1 Patients' characteristics

	All patients ($n=41$)	
	No. of patients	%
Sex		
Male	24	58.5
Female	17	41.5
Age (years) Median [range]	67 [43–80]	
ECOG-PS		
0	29	70.7
1	11	26.8
2	1	2.4
Primary site		
Colon	23	56.1
Rectum	18	43.9
Metastatic site		
Liver	29	70.7
Lung	21	51.2
Lymph node	11	26.8
Bone	1	2.4
Peritoneum	6	14.6
Others	4	9.8
Operation for primary lesion	40	97.6
Histology		
Well	4	9.8
Moderately	30	73.2
Papillary	3	7.3
Mucinous	4	9.8
K-RAS		
Wild	23	56.1
Mutation	18	43.9
Treatment line		
Third	15	36.6
Fourth or later	26	63.4
Prior L-OHP-based therapy		
FOLFOX	26	63.4
XELOX	13	31.7
SOX	2	4.9
Discontinuation reason		
Refractory	30	73.2
Intolerance	8	19.5
Planned stop	3	7.3
S-1 treatment schedule		
Biweekly	32	78
Alternative-day	9	22
Bevacizumab	29	70.7

Efficacy endpoints

Forty patients experienced an event of PFS as the primary endpoint. The median PFS, TTF and OS were 3.3 months

(95% CI 2.7–4.2), 2.4 months (95% CI 1.8–3.2) and 10.1 months (95% CI 8.3–14.6), respectively (Fig. 2). A complete response (CR), partial response (PR), stable disease (SD) or progression disease (PD) of the target lesions was observed in 0, 4, 22 and 14 cases, respectively; the response rate and disease control rate were 10.0% and 65.0%, respectively.

Safety outcomes

The median RDIs of oxaliplatin and S-1 were 80.6% (interquartile range 75.0–94.4%) and 85.6% (interquartile range, 75.0–100.0%), respectively. The treatment-related AEs are summarized in Table 2. The most common grade 3 AEs were thrombocytopenia (5.0%), anorexia (5.0%), fatigue (5.0%) and pneumonia (5.0%). There was no case of grade 4 AE or treatment-related death.

Discussion

In this present study, our hypothesis that biweekly SOX as a third-or-later-line regimen for mCRC could secure a PFS of 3.5 months was proven. In addition, the AE profile was acceptable compared with previous trials. Given these findings, we consider this test regimen to be a useful potential option for treating mCRC.

Our results show that the PFS of biweekly SOX was 3.3 months (95% CI 2.7–4.2). This outcome is better than that of best supportive care or molecular-targeted monotherapy according to the results of trials for panitumumab, cetuximab and regorafenib [19–21]. The effectiveness of cytotoxic doublets was confirmed in the present study, suggesting that we should consider the reintroduction of oxaliplatin as a third-or-later-line regimen.

Although the clinical significance of combination therapy with S-1 is still being examined, the outcome of S-1 therapy might be better in patients who have received first-line oxaliplatin therapy than in those who have not, based on the results of the FIRIS study [10], a phase II/III trial that proved the noninferiority of irinotecan plus S-1 to FOLFIRI with regard to the PFS. In addition, the basic analyses of that study showed that the ERCC1 and DPD levels were significantly higher in patients who received oxaliplatin than in those with no history of oxaliplatin administration [23]. From this perspective, S-1 is thus considered to have a superior activity against DPD-high lesions, and therefore this treatment regimen may achieve a better survival than other 5-FU drugs in the oxaliplatin reintroduce regimen. Furthermore, Hong et al. reported a better outcome of SOX as the first-line treatment for mCRC than treatment with the XELOX regimen (8.5 versus 6.7 months) in an Asian population in a randomized phase III trial designed to prove the noninferiority of SOX

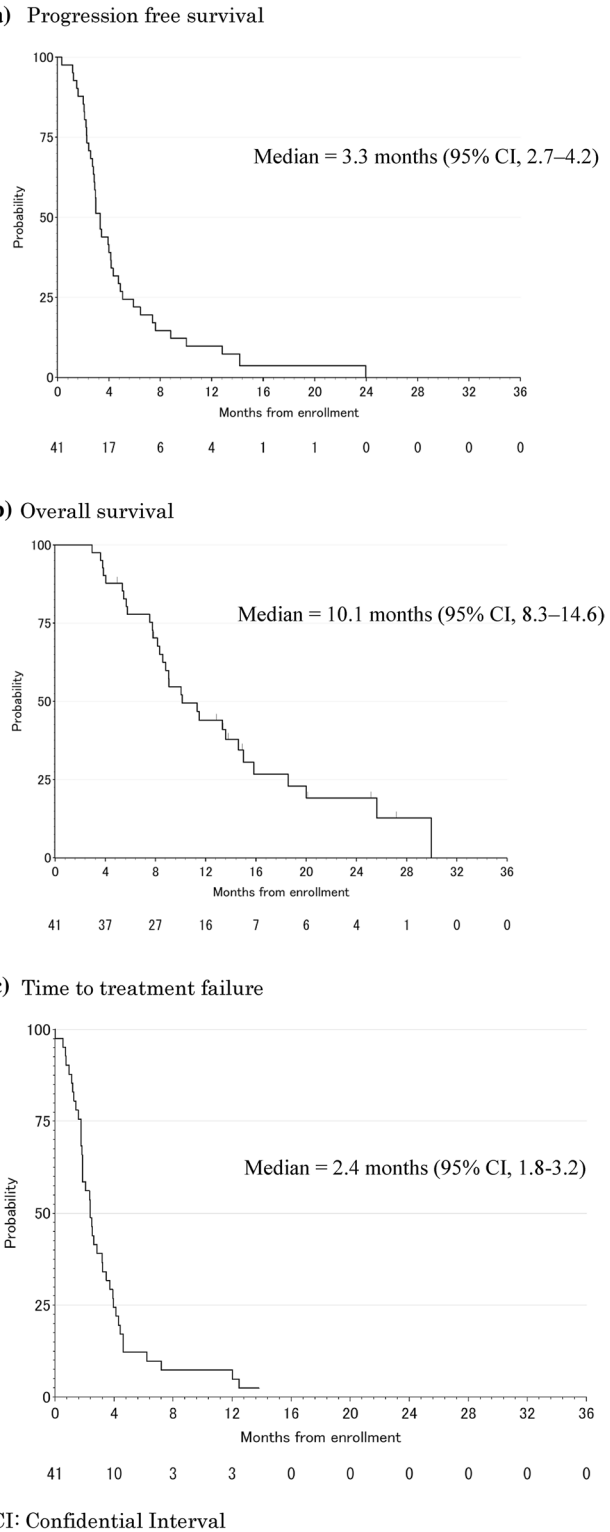

Fig. 2 Survival outcomes of biweekly SOX as third or later-line. **a** Progression-free survival. The median was 3.3 months (95% confidential interval, 2.7–4.2). **b** Overall survival. The median was 10.1 months (95% confidential interval, 8.3–14.6). **c** Time to treatment failure. The median was 2.4 months (95% confidential interval, 1.8–3.2)

Table 2 Adverse events

	All grade		≥ Grade 3	
	$n=40$	%	$n=40$	%
Neutropenia	6	15.0	1	2.5
Anemia	26	65.0	1	2.5
Thrombocytopenia	24	60.0	2	5.0
Proteinuria	3	7.5	1	2.5
Peripheral neuropathy	38	95.0	0	0.0
Hand–foot syndrome	8	20.0	0	0.0
Allergy	10	25.0	1	2.5
Nausea	19	47.5	1	2.5
Anorexia	22	55.0	2	5.0
Fatigue	34	85.0	2	5.0
Diarrhea	15	37.5	0	0.0
Vomiting	6	15.0	1	2.5
Mucositis or stomatitis	7	17.5	0	0.0
Pneumonia	2	5.0	2	5.0
Alopecia	8	20.0	0	0.0

to XELOX [11]. Based on these results, SOX has been one of recommended options according to the Asian-adopted ESMO consensus guidelines [1].

There were no severe hematologic toxicities or peripheral neuropathy in the present study. These results seem to be considerably better than those reported with a triweekly SOX regimen in previous trials, although no direct comparison was made between biweekly and triweekly regimens. The control of adverse events and a good general condition are required for patients with mCRC, maintaining RDI during treatments. Therefore, the biweekly SOX regimen used in the present study may therefore be the optimal choice for these patients as a third-or-later-line regimen.

This study was a single-arm and small-scale phase II study, as it is difficult to enroll subjects in trials to evaluate the effectiveness of cytotoxic drugs in the third or later line. The efficacy and safety of biweekly SOX based solely on our study results remain difficult to interpret; however, this trial was the first to reveal the oncological impact of biweekly SOX as oxaliplatin reintroduction therapy for mCRC and has provided meaningful data for physicians. The efficacy of combination therapy with molecular-targeted drugs should be evaluated in further studies with consideration of gene mutation profiles and the site of the primary lesion.

In conclusion, the biweekly SOX regimen for the reintroduction of oxaliplatin seems promising for improving the PFS without serious AEs in patients with mCRC.

Acknowledgements This work was supported, in part, by a non-profit organization, Epidemiological and Clinical Research Information Network (ECRIN).

Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

References

1. Yoshino T, Arnold D, Taniguchi H et al (2018) Pan-Asian adapted ESMO consensus guidelines for the management of patients with metastatic colorectal cancer: a JSMO-ESMO initiative endorsed by CSCO, KACO, MOS, SSO and TOS. Ann Oncol Off J Eur Soc Med Oncol ESMO 29(1):44–70. https://doi.org/10.1093/annonc/mdx738
2. Chen D, Li L, Zhang X et al (2018) FOLFOX plus anti-epidermal growth factor receptor (EGFR) monoclonal antibody (mAb) is an effective first-line treatment for patients with RAS-wild left-sided metastatic colorectal cancer: a meta-analysis. Medicine 97(10):e0097. https://doi.org/10.1097/md.0000000000010097
3. Brule SY, Jonker DJ, Karapetis CS et al (2015) Location of colon cancer (right-sided versus left-sided) as a prognostic factor and a predictor of benefit from cetuximab in NCIC CO.17. Eur J Cancer (Oxf Engl 1990) 51(11):1405–1414. https://doi.org/10.1016/j.ejca.2015.03.015
4. Karapetis CS, Khambata-Ford S, Jonker DJ et al (2008) K-ras mutations and benefit from cetuximab in advanced colorectal cancer. N Engl J Med 359(17):1757–1765. https://doi.org/10.1056/NEJMoa0804385
5. Tournigand C, Andre T, Achille E et al (2004) FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. J Clin Oncol Off J Am Soc Clin Oncol 22(2):229–237. https://doi.org/10.1200/jco.2004.05.113
6. de Gramont A, Figer A, Seymour M et al (2000) Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. J Clin Oncol Off J Am Soc Clin Oncol 18(16):2938–2947
7. de Gramont A, Buyse M, Abrahantes JC et al (2007) Reintroduction of oxaliplatin is associated with improved survival in advanced colorectal cancer. J Clin Oncol Off J Am Soc Clin Oncol 25(22):3224–3229. https://doi.org/10.1200/JCO.2006.10.4380
8. Tournigand C, Cervantes A, Figer A et al (2006) OPTIMOX1: a randomized study of FOLFOX4 or FOLFOX7 with oxaliplatin in a stop-and-Go fashion in advanced colorectal cancer—a GERCOR study. JJ Clin Oncol Off J Am Soc Clin Oncol 24(3):394–400. https://doi.org/10.1200/JCO.2005.03.0106
9. Grothey A (2010) Reintroduction of oxaliplatin: a viable approach to the long-term management of metastatic colorectal cancer. Oncology 79(5–6):389–399. https://doi.org/10.1159/000323491
10. Muro K, Boku N, Shimada Y et al (2010) Irinotecan plus S-1 (IRIS) versus fluorouracil and folinic acid plus irinotecan (FOLFIRI) as second-line chemotherapy for metastatic colorectal cancer: a randomised phase 2/3 non-inferiority study (FIRIS study). Lancet Oncol 11(9):853–860. https://doi.org/10.1016/s1470-2045(10)70181-9
11. Hong YS, Park YS, Lim HY et al (2012) S-1 plus oxaliplatin versus capecitabine plus oxaliplatin for first-line treatment of patients with metastatic colorectal cancer: a randomised, non-inferiority phase 3 trial. Lancet Oncol 13(11):1125–1132. https://doi.org/10.1016/S1470-2045(12)70363-7
12. Yamada Y, Takahari D, Matsumoto H et al (2013) Leucovorin, fluorouracil, and oxaliplatin plus bevacizumab versus S-1 and oxaliplatin plus bevacizumab in patients with metastatic colorectal cancer (SOFT): an open-label, non-inferiority, randomised phase

3 trial. Lancet Oncol 14(13):1278–1286. https://doi.org/10.1016/s1470-2045(13)70490-x
13. Oki E, Emi Y, Miyamoto Y, Kabashima A et al (2015) Phase II trial of S-1 and oxaliplatin plus cetuximab for colorectal cancer patients with initially unresectable or not optimally resectable liver metastases (KSCC1002). Ann Surg Oncol 22(Suppl 3):S1067–S1074. https://doi.org/10.1245/s10434-015-4771-1
14. Baba H, Yamada Y, Takahari D et al (2017) S-1 and oxaliplatin (SOX) plus bevacizumab versus mFOLFOX6 plus bevacizumab as first-line treatment for patients with metastatic colorectal cancer: updated overall survival analyses of the open-label, non-inferiority, randomised phase III: SOFT study. ESMO Open 2(1):e000135. https://doi.org/10.1136/esmoopen-2016-000135
15. Hong J, Han SW, Ham HS et al (2011) Phase II study of biweekly S-1 and oxaliplatin combination chemotherapy in metastatic colorectal cancer and pharmacogenetic analysis. Cancer Chemother Pharmacol 67(6):1323–1331. https://doi.org/10.1007/s00280-010-1425-7
16. Ogawa M, Anan T, Suzuki T et al (2016) Initial report of phase ii study on bi-weekly SOX plus cetuximab treatment for wild-type K-RAS advanced and recurrent colorectal cancer. Anticancer Res 36(5):2505–2511
17. Matsuda C, Honda M, Tanaka C et al (2016) Multicenter randomized phase II clinical trial of oxaliplatin reintroduction as a third- or later-line therapy for metastatic colorectal cancer-biweekly versus standard triweekly XELOX (the ORION study). Int J Clin Oncol 21(3):566–572. https://doi.org/10.1007/s10147-015-0911-7
18. Eisenhauer EA, Therasse P, Bogaerts J et al (2009) New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer (Oxf Engl 1990) 45(2):228–247. https://doi.org/10.1016/j.ejca.2008.10.026
19. Kuboki Y, Nishina T, Shinozaki E et al (2017) TAS-102 plus bevacizumab for patients with metastatic colorectal cancer refractory to standard therapies (C-TASK FORCE): an investigator-initiated, open-label, single-arm, multicentre, phase 1/2 study. Lancet Oncol 18(9):1172–1181. https://doi.org/10.1016/s1470-2045(17)30425-4
20. Jonker DJ, O'Callaghan CJ, Karapetis CS et al (2007) Cetuximab for the treatment of colorectal cancer. N Engl J Med 357(20):2040–2048. https://doi.org/10.1056/NEJMoa071834
21. Van Cutsem E, Kohne CH, Hitre E et al (2009) Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. N Engl J Med 360(14):1408–1417. https://doi.org/10.1056/NEJMoa0805019
22. Suenaga M, Mizunuma N, Matsusaka S et al (2015) Phase II study of reintroduction of oxaliplatin for advanced colorectal cancer in patients previously treated with oxaliplatin and irinotecan: RE-OPEN study. Drug Des Dev Ther 9:3099–3108. https://doi.org/10.2147/dddt.s85567
23. Baba H, Watanabe M, Okabe H et al (2012) Upregulation of ERCC1 and DPD expressions after oxaliplatin-based first-line chemotherapy for metastatic colorectal cancer. Br J Cancer 107(12):1950–1955. https://doi.org/10.1038/bjc.2012.502

Affiliations

Hiroaki Tanioka[1] · Michitaka Honda[2] · Chihiro Tanaka[3] · Yoshitaka Morita[4] · Keiichiro Ishibashi[5] · Takeshi Kato[6] · Chu Matsuda[7] · Masato Kataoka[8] · Hironaga Satake[9] · Yoshinori Munemoto[10] · Kenji Kobayashi[11] · Masazumi Takahashi[12] · Ken Nakata[13] · Junichi Sakamoto[14] · Koji Oba[15] · Hideyuki Mishima[16]

1 Department of Clinical Oncology, Kawasaki Medical School, Kurashiki, Japan
2 Department of Minimally Invasive Surgical and Medical Oncology, Fukushima Medical University, 1 Hikarigaoka, Fukushima, Fukushima 960-1295, Japan
3 Department of Surgery, Gifu Prefectual General Medical Center, Gifu, Japan
4 Department of Radiology, National Hospital Organization Kobe Medical Center, Kobe, Japan
5 Department of Digestive Tract and General Surgery, Saitama Medical Center, Saitama Medical University, Saitama, Japan
6 Department of Surgery, Kansai Rosai Hospital, Amagasaki, Japan
7 Department of Gastroenterological Surgery, Graduate School of Medicine, Osaka University, Osaka, Japan
8 Department of Surgery, Naogoya Medical Center, Nagoya, Japan
9 Department of Medical Oncology, Kobe City Medical Center General Hospital, Kobe, Japan
10 Department of Surgery, Fukui Saiseikai Hospital, Fukui, Japan
11 Department of Surgery, Matsunami General Hospital, Gifu, Japan
12 Department of Surgery, Yokohama Municipal Citizen's Hospital, Yokohama, Japan
13 Department of Surgery, Sakai City Medical Center, Sakai, Japan
14 Tokai Central Hospital, Kagamigahara, Japan
15 Department of Biostatistics, The University of Tokyo School of Public Health, Tokyo, Japan
16 Cancer Center, Aichi Medical University, Aichi, Japan