Initial Report of Phase II Study on Bi-weekly SOX plus Cetuximab Treatment for Wild-type *K-RAS* Advanced and Recurrent Colorectal Cancer

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Abstract. *Aim: This prospective study was designed to evaluate the tolerability and the efficacy of bi-weekly SOX (S-1 and oxaliplatin)+cetuximab as first-line chemotherapy for wild-type K-RAS metastatic colorectal cancer. Patients and Methods: We studied patients with previously untreated, unresectable, advanced or recurrent colorectal cancer who were treated in our hospital between October 2010 and March 2013. Their performance status (PS) was 0 to 1. Cetuximab was combined with S-1 and oxaliplatin (SOX+cetuximab). S-1 was given orally at a dose of 40 mg/m^2 (40-60 mg, calculated according to body surface area) twice daily after meals for 2 weeks, followed by a 2-week rest (course 1). Oxaliplatin (85 mg/m^2) was given on days 1 and 15 of each course. Cetuximab was administered on days 1 (400 mg/m^2), 8 (250 mg/m^2) and 15 (500 mg/m^2) of course 1, followed by every 2 weeks (500 mg/m^2) thereafter. Results: The study group comprised of 18 patients. The mean age was 61 (range=32-72) years, the male:female ratio was 10:8 and the PS was 0 in 12 patients and 1 in 6 patients. The median number of administered courses was 6 (range=2-12). The treatment response was complete response (CR) in 2 and partial response (PR) in 10 (response rate=67% (12/18 patients)). The minimum number of treatment courses until a PR was 2, indicating an early response. Liver resection was performed in 4 patients (22.2%). The incidence of any adverse events (Grade 3/4) was 28% (5/18), including skin disorder (16.7%) as dry skin, cutaneous pruritus, contusion and paronychia, as well as peripheral sensory neuropathy (11.1%). The any-grade events of skin disorders and peripheral sensory neuropathy were mostly observed in all patients. These events were controllable by preventive skin care and by withdrawal and dose reduction, respectively. Death due to adverse events was not observed. Adverse events did not require the withdrawal of this regimen. Conclusion: Based on the 18 patients studied, combined therapy with SOX+cetuximab was free of serious adverse events and could be safely administered by reducing the dose or temporarily suspending treatment, as required. These regimens seem to be promising for conversion therapy (4 out of 18 patients) because of good outcomes and an early response.*

Cetuximab is a monoclonal antibody that locks the epidermal growth factor receptor (EGFR). The efficacies of cetuximab for patients with wild-type *K-RAS* have been evaluated and reported in the CRYSTAL, OPUS and CELIM trials (1-3) In the CRYSTAL trial, which is the most known trial, the additional effect of cetuximab to FOLFIRI has been demonstrated. Additionally, the favorable effect of cetuximab to FOLFOX for the wild type *K-RAS* has been demonstrated in both the OPUS and the CELIM trials. Both trials have gained attention because the conversion therapy became popular recently. For the bi-weekly administration of cetuximab, some Phase II trials have been reported. In the ASCO 2011, the same efficacy has been reported in response rate (RR) and progression-free survival (PFS) of bi-weekly regimen compared to weekly regimen. In recent clinical trials, it has been suggested that the RRs of cetuximab combined with FOLFIRI and FOLFOX were better than those of an antivascular endothelial growth factor antibody combination with chemotherapy for patients with the wild-type extended *RAS* populations beyond the *K-RAS* exon2 wild-type (4, 5). S-1 is a novel oral fluoropyrimidine derivative consisting of 1 M tegafur as a prodrug of 5-fluorouracil (5-FU), 0.4 M of gimeracil (CDHP) and 1 M of oteracil potassium (Oxo). CDHP enhances the anti-tumor effect of 5-FU by strongly inhibiting the dihydropyrimidine dehydrogenase (DPD) and elevates the concentration of

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5-FU in blood and tumor tissues. Oxo localizes in the intestinal mucosa and reduces digestive toxicities caused by an increase of the 5-FU concentration. Thus, S-1 has an excellent anti-tumor effect compared to conventional infusional 5-FU and simultaneously decreases the side effects for increasing the 5-FU concentration (6-8). In Japan, S-1 was approved for the seven kinds of carcinomas, including gastric cancer, colorectal cancer, *etc*. Late phase II studies of patients with advanced or recurrent colorectal cancer have reported a RR of 37.4% in patients with advanced or recurrent colorectal cancer (9, 10).

The efficacies and the safety data of the SOX treatment, which were combined with S-1 plus oxaliplatin (L-OHP), have been reported for the advanced recurrent colorectal cancer in two Phase II and one Phase III trials. This Phase III study was performed in Korea and showed the non-inferiority of SOX to COX, which is Xeloda and L-OHP combination. PFS, as the primary end-point, was evaluated not only for non-inferiority of SOX but also for its superiority (11-13). However, the combination of SOX plus cetuximab has not been investigated for colorectal cancer (CRC) patients with initially unresectable tumors. The goal of this prospective study was to evaluate the tolerability and the efficacy of bi-weekly SOX and cetuximab combination therapy as first-line chemotherapy for metastatic colorectal cancer with wild type *K-RAS*. The primary end-point was RR, while secondary endpoints were adverse events (AE), overall survival (OS), time to progression (TTP), progression-free survival (PFS), compliance, RR by disease (metastatic site, grade of skin toxicity). In this initial report, we report RR, AE and liver resection rate.

Patients and Methods

Patients. All patients enrolled in this study met the following eligibility criteria: (i) a histologically proven diagnosis of adenocarcinoma of the colon or rectum; (ii) aged over 20 years and under 75 years; (iii) Eastern Cooperative Oncology Group performance status (ECOG PS) 0 to 1; (iv) wild-type *K-RAS* and unresectable advanced/recurrent colorectal cancer, excluding tumor in the vermiform processus and proctos; (v) no prior chemotherapy; (vi) adequate organ function (white blood cells (WBCs) 3,500 and 12,000/mm^3, neutrophils 1,500/mm^3, hemoglobin 9.0 g/dl, platelets 100,000/mm^3, total serum bilirubin 1.5 mg/dl, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) 2.0-times the respective upper limits of normal, serum creatinine within the upper limit of normal range or creatinine clearance 60 ml/min); (vii) estimated life expectancy over 3 months.

This study was approved by an institutional ethics committee, while informed consent was obtained from all enrolled patients.

Chemotherapy. The treatment schedule comprised oral S-1 40 to 60 mg/body twice daily for 2 weeks, infusion of oxaliplatin 85 mg/m^2 on day 1 and day 15 repeated every 4 weeks, infusion of cetuximab of 400 mg/m^2 250 mg/m^2, 500 mg/m^2 on day 1, 8, 15 at the first cycle, followed by 500 mg/m^2 repeated every 2 weeks. In addition, treatment was started within 28 days after the registration date and was repeated every 4 weeks per cycle until the onset of disease progression or severe toxicity (Figure 1). Serum and clinical examinations were performed bi-weekly whenever possible during the first course of treatment (at least once every 2 weeks). From the second course of treatment onward, examinations were done at least once every 2 weeks (standard schedule) or at least once every 4 weeks. After the second course of treatment, all patients underwent radiography, computed tomography (CT), magnetic resonance imaging (MRI) or ultrasonography to check for recurrence. However, it was evaluated by CT if the carcinoembryonic antigen (CEA) value at the end of first course of treatment is rapidly reduced. Adverse reactions were evaluated according to the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCICTCAE, ver. 2). The rates of AEs were calculated for the period of every course.

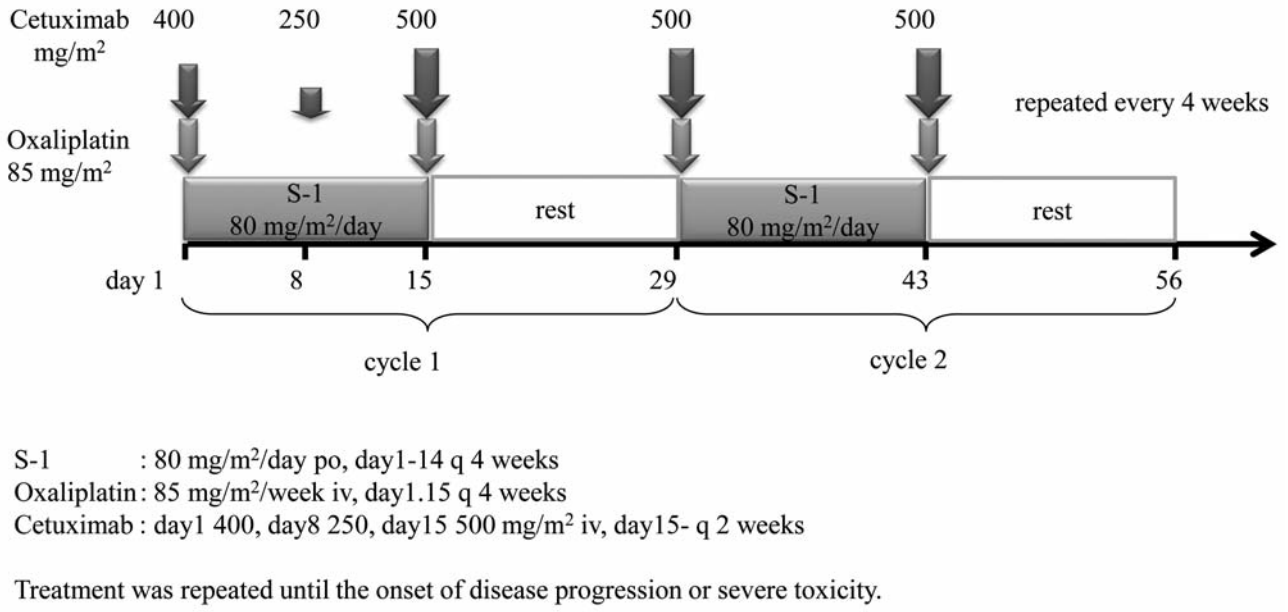
Resection criteria. Liver resection is preferred within the limits of evading liver failure after operation, excluding organ metastasis except lung, local reccurence and para-aortic lymph node metastasis. Our strategy of liver resection for colorectal cancer liver metastases follows: a) Hepatic lobectomy is allowed in case of indocyanine green (ICG) 15 min≤20%, b) percutaneous transhepatic portal embolization (PTPE) is performed in advance in case of rate of liver remnant in volumetry≤30%, c) non-cancerous part is conserved to the maximum extent, d) the lesion's clinical complete response (cRC) is kept if unable to be proved by ultrasound in operation

Results

Patients' characteristics. From October 2010 to March 2013, 18 patients with previously untreated, unresectable, advanced or recurrent colorectal cancer who were treated in our hospital were enrolled in this study (Table I). The median age was 61 years (range=32-72). The patients with ECOG PS 0 were 12 and PS 1 were 6. Seven patients had primary tumor sites in the colon and other 11 patients in the rectum. All patients had liver metastasis, 5 patients in the lung, 2 patients in the ovary, 2 patients in the peritoneum and 8 patients in the lymph nodes. Only liver metastasis without multiple organ metastasis was found in 15 patients.

Adverse Events (AEs). (i) Hematologic toxicity: Toxicity was assessed according to the Common Terminology Criteria for Adverse Events v4.0. leukopenia was observed in 44% (8/18), thrombocytopenia was observed in 61% (11/18) and AST/ALT elevation was observed in over 50%. However, there was only one case (1/18) where toxicity was greater than G3 but the regimen was considered well-tolerated (Table II).

(ii) Non-hematologic toxicity: Regarding non-hematologic toxicity, skin reactions associated with cetuximab were observed in most of the patients, whereas more than G3 dry skin, pruritus and rash acneiform were observed in 3 patients. Peripheral neuropathy due to L-OHP was observed in most patients, but grade 3/4 neuropathy was occurred in only 2 patients. Moreover, the rates of gastrointestinal toxicity were comparatively low and more than G3 was not observed (Table III).



S-1 : 80 mg/m²/day po, day1-14 q 4 weeks
Oxaliplatin : 85 mg/m²/week iv, day1.15 q 4 weeks
Cetuximab : day1 400, day8 250, day15 500 mg/m² iv, day15- q 2 weeks

Treatment was repeated until the onset of disease progression or severe toxicity.

Figure 1. *The treatment schedule comprised oral S-1 40 to 60 mg/body twice daily for 2 weeks, infusion of oxaliplatin 85 mg/m² on day 1 and day 15 repeated every 4 weeks and infusion of cetuximab of 400 mg/m², 250 mg/m², 500 mg/m² on day 1, 8, 15 at the first cycle, followed by 500 mg/m² repeated every 2 weeks. In addition, treatment was started within 28 days after the registration date and was repeated every 4 weeks per cycle until the onset of disease progression or severe toxicity.*

Table I. *Patient's characteristics.*

Characteristics		N=18
Age	Mean	61
	(Range)	(32-72)
ECOG PS		
	0	12
	1	6
Gender	Male	10
	Female	8
Site of primary tumor	Colon:inc. Rs*	7
	Rectum	11
Site of metastatic organ	Liver	18
	Lung	5
	Ovary	2
	Peritoneum	2
	Lymph nodes	8

*Included recto-sigmoid colon.

Table II. *Adverse Events (hematologic toxicity).*

N=18	CTCAE v4.0					
	Grade (CTCAE ver4.0)				All grade ≥G3	
	1	2	3	4	(%)	(%)
Leukopenia	7	1			44	
Neutropenia	1	1			11	
Thrombocytopenia	7	4			61	
Anemia	5	1			33	
AST	13		1		78	6
ALT	10		1		61	6
Total bilirubin elevation	2	1		1	22	6

AST: Aspartate transaminase, ALT: alanine transaminase.

Efficacy. All responses were defined according to the RECIST version 1.1. Complete response (CR) and partial response (PR) were observed in 2 and 10 patients, respectively. Response rate (RR) was 67% and disease control rate (DCR) was 89%. The entire evaluable region for RR was liver and the median duration to PR-in was 42 days. Liver resection rate was 22.2% but it became 33.3% when CR was considered to be a liver metastasis control. This rate was extremely high and satisfactory. The durations to CR-in of 2 patients were 140 days and 98 days, respectively. And the median treatment cycles were 6 (Table IV).

Table III. *Adverse events (non-hematologic toxicity).*

N=18	CTCAE v4.0				
	Grade (CTCAE ver4.0)				All grade ≥G3
	1	2	3	4 (%)	(%)
Anorexia	2	4		33	
Fatigue	5	4		50	
Constipation	3			17	
Nausea	6	2		44	
Diarrhea	4	2	1	39	6
Mucositis oral	7	2		50	
Dry skin	1	7	2	56	11
Rash acneiform	7	4	3	78	17
Pruritus	4	2	1	39	6
Nail discoloration					
Paronychia	8	4	1	72	6
Alopecia	1			6	
Skin hyperpigmentation		1		6	
Peripheral neuropathy	8	5	2	83	11

Table IV. *Response rate and liver resectability.*

Response rate and liver resectability	N=18	%	Median days (interval)
CR	2		
PR	10		
SD	4		
PD	2		
NE	0		
CR+PR	12	67 (RR)	
CR+PR+SD	16	89 (DCR)	
Liver resection	4	22	
Liver control (resection + CR)	6	33	
The duration to PR-in			42 (28-108)

CR: Complete response, PR: partial response, SD: stable disease, PD: progressive disease, NE: not evaluated.

Discussion

Based on previous clinical studies (14-16), bevacizumab plus standard regimens, such as FOLFOX, CapeOX and FOLFIRI, are currently recommended as first-line treatment for metastatic colorectal cancer (mCRC). Some clinical Phase II trials using the above regiments reported RRs in the range of 42-78% (17-20). In Japan, the results of Phase II studies evaluating S-1 plus irinotecan combined with bevacizumab as first-line treatment report RRs in the range of 57.7-72% (21-23).

Thus, recent results of Phase II studies evaluating SOX with cetuximab as first-line treatment have reported a RR of 63.6% (24). The RR in our study (67%) is not favorably compared to previous studies.

Hand-foot-skin reaction (HFSR) is regarded as one of the most important AEs of capecitabine with an incidence of 20-60%. In the X-ACT trial (Xeloda: 2,500 mg/m^2), the rate of HFSR was 61.1% (n=613 out of 1,004 patients) (25). Also, in the CIOX trial (Xeloda: 1,600 or 2,000, mg/m^2), the rate of HFSR reported was 30.2 % (n=198/655) (26). Suppression of the EGFR signaling pathway injures keratinocytes by inducing growth arrest and apoptosis, decreasing cell migration, increasing cell attachment, cell differentiation and stimulating inflammatory chemokine expression (27). A number of previous articles have reported on the expression and localization of EGFR and EGFR ligands in human skin and the phenotypes of knockout and transgenic mice developed to analyze the *in vivo* function of the EGFR/ligand system in the skin (28). In the COIN trial, cetuximab was shown to have severe skin toxicity (29, 30). On the other hand, S-1 has been reported to be less toxic considering skin toxicity (31).

In our study, regarding non-hematologic toxicity, no new safety concerns, including HFSR, were observed. Skin reactions associated with cetuximab were observed in most patients, while more than G3 dry skin, pruritus and rash acneiform were observed in 3 patients. Peripheral neuropathy due to L-OHP was observed in most of the patients, but Grade 3/4 neuropathy was occurred in only 2. Moreover, the rates of gastrointestinal toxicity were comparatively low and more than G3 was not observed.

According to the hematologic toxicity, leukopenia was observed in 44%, thrombocytopenia was observed in 61% and AST/ALT elevation was observed in over 50% of cases. However, there was only one case (1/18) with greater than G3 toxicity; however, this regimen was considered well-tolerated. Therefore, the combination of SOX with cetuximab appears to be a new candidate regimen for mCRC patients.

The resection rate of this study was 22.2%; however, it became 33.3% when CR was considered to be a liver metastatic disease control. In 15 patients with only liver metastasis, without multiple organ metastases, the resection rate was 26.6%. Some clinical Phase II trials have examined the use of FOLFOX6 or CapeOX with bevacizumab and investigated the potential for resectability in mCRC with liver metastases. Although the R0 resection rates were 20-36% (17-20), the R0 resection rate after FOLFIRI plus cetuximab chemotherapy in the CRYSTAL study was 7.0% and the rate after FOLFOX plus cetuximab in the OPUS study was 9.8%. On the other hand, the CELIM study used cetuximab for

unresectable mCRC and showed that the R0 rate was 38% in the FOLFOX6 plus cetuximab arm of the study. This R0 rate was similar to our results suggesting that the cetuximab with cytotoxic chemotherapy is a good combination for liver metastasis resection. Recently, a clinical Phase II trial in Japan examined the use of SOX with cetuximab and investigated the potential for resectability in mCRC with liver metastases. The overall resection rate was 48.5 % (16/33; 95% confidence interval (CI)=30.8-66.5), while the macroscopic R0 resection rate was 39.4% (13/33; 95%CI=22.9-57.9). Histological curability was performed in 13/16 using R0; in 2/16 using R1; and in 1/16 using R2 (24). Nevertheless, our resection rate was extremely high and satisfactory.

It has been reported that the rate of early tumor shrinkage (ETS) is directly associated with the ability to operate (32). It might be suggested that patients who respond quickly to a treatment may experience better outcomes than those with slower response or disease stabilization. To verify if faster tumor shrinkage may be used as a prognostic factor, a retrospective analysis of 113 irinotecan-refractory patients enrolled in four clinical trials (BOND, EVEREST, SALVAGE and BABEL) not only showed that the decrease in tumor size was greater in wild-type K-RAS patients when compared to mutants, but also that the rapid tumor shrinkage correlated with a better outcome (33). In particular, patients with a tumor size decrease of at least 10% at the 6-week radiological assessment had a median PFS of 36 weeks compared to 12 weeks in patients who did not exhibit an early tumor response ($p<0.001$). ETS was a strong predictor for survival (hazard ratio (HR)=0.42) (33). A retrospective analysis of CRYSTAL and OPUS trials showed a significant association between ETS (in this case, defined as an early shrinkage of at least 20%) and PFS in patients exposed to cetuximab (34). This retrospective analysis showed that early tumor assessments might provide predictive information for long-term outcome of metastatic CRC patients exposed to first-line chemotherapy in combination with cetuximab. Although a number of studies suggest that ETS has a potential value in CRC patients, it is possible that some patients, who partially respond early, may become complete responders at subsequent examinations, further complicating the interpretation of the results. In our study, the median duration to PR-in was 42 days, which is the most characteristic point of this regimen. However, even if a maximal tumor shrinkage is not the result of the primary treatment purpose in all cases of mCRC patients, a complete disease removal after downsizing by chemotherapy may give the potential of long-term survival or cure in potentially resectable metastatic patients.

Conclusion

From the 18 patients evaluated, the combination therapy of SOX+cetuximab showed no serious AEs and could be safely administered. The combination therapy of SOX+cetuximab demonstrated a beneficial effect and fast response. Therefore, SOX+cetuximab appears as a first-line chemotherapy regimen, which is characterized by ETS and early PR, that is suitable for cases aiming at converting liver metastasis.

Conflicts of Interest

The Authors declare that they have no conflict of interest.

References

1 Van Cutsem E, Köhne CH, Hitre E, Zaluski J, Chang Chien CR, Makhson A, D'Haens G, Pintér T, Lim R, Bodoky G, Roh JK, Folprecht G, Ruff P, Stroh C, Tejpar S, Schlichting M, Nippgen J and Rougier P: Cetuximab and Chemotherapy as Initial Treatment for Metastatic Colorectal Cancer. N Engl J Med *360*: 1408-1417, 2009.

2 Bokemeyer C, Bondarenko I, Makhson A, Hartmann JT, Aparicio J, de Braud F, Donea S, Ludwig H, Schuch G, Stroh C, Loos AH, Zubel A and Koralewski P: Fluorouracil, Leucovorin, and Oxaliplatin With and Without Cetuximab in the First-Line Treatment of Metastatic Colorectal Cancer. J Clin Oncol *27(5)*: 663-671, 2008.

3 Folprecht G, Gruenberger T, Bechstein WO, Raab HR, Lordick F, Hartmann JT, Lang H, Frilling A, Stoehlmacher J, Weitz J, Konopke R, Stroszczynski C, Liersch T, Ockert D, Herrmann T, Goekkurt E, Parisi F and Köhne CH: Tumour response and secondary resectability of colorectal liver metastases following neoadjuvant chemotherapy with cetuximab: the CELIM randomised phase 2 trial. Lancet Oncol *11*: 38-47, 2010.

4 Heinemann V, von Weikersthal LF, Decker T, Kiani A, Vehling-Kaiser U, Al-Batran SE, Heintges T, Lerchenmüller C, Kahl C, Seipelt G, Kullmann F, Stauch M, Scheithauer W, Hielscher J, Scholz M, Müller S, Link H, Niederle N, Rost A, Höffkes HG, Moehler M, Lindig RU, Modest DP, Rossius L, Kirchner T, Jung A and Stintzing S: FOLFIRI plus cetuximab *versus* FOLFIRI plus bevacizumab as first-line treatment for patients with metastatic colorectal cancer (FIRE-3): a randomised, openlabel, phase 3 trial. Lancet Oncol *15*: 1065-1075, 2014.

5 Van Cutsem E, Lenz HJ, Köhne CH, Heinemann V, Tejpar S, Melezínek I, Beier F, Stroh C, Rougier P, van Krieken JH and Ciardiello F: Fluorouracil, leucovorin, and irinotecan plus cetuximab treatment and RAS mutations in colorectal cancer. J Clin Oncol *33*: 692-700, 2015.

6 Shirasaka T, Shimamato Y, Ohshimo H, Yamaguchi M, Kato T, Yonekura K and Fukushima M: Development of a novel form of an oral 5-fluorouracil derivative (S-1) directed to the potentiation of the tumor selective cytotoxicity of 5-fluorouracil by two biochemical modulators. Anticancer Drugs *7*: 548-557, 1996.

7 Diasio RB: Clinical implications of dihydropyrimidine dehydrogenase inhibition. Oncology (Williston Park) *13*: 17-21, 1999.

8 Yamada Y, Hamaguchi T, Goto M, Muro K, Matsumura Y, Shimada Y, Shirao K and Nagayama S: Plasma concentrations of 5-fluorouracil and F-b-alanine following oral administration of S-1, a dihydropyrimidine dehydrogenase inhibitory fluoropyrimidine, as compared with protracted venous infusion of 5-fluorouracil. Br J Cancer *89*: 816-820, 2003.

9 Ohtsu A, Baba H, Sakata Y, Mitachi Y, Horikoshi N, Sugimachi K and Taguchi T: Phase II study of S-1, a novel oral fluoropyrimidine derivative, in patients with metastatic colorectal carcinoma. S-1 Cooperative Colorectal Carcinoma Study Group. Br J Cancer *83*: 141-145, 2000.

10 Shirao K, Ohtsu A, Takada H, Mitachi Y, Hirakawa K, Horikoshi N, Okamura T, Hirata K, Saitoh S, Isomoto H and Satoh A: Phase II study of oral S-1 for treatment of metastatic colorectal carcinoma. Cancer *100*: 2355-2361, 2004.

11 Zang DY, Lee BH, Park HC, Song HH, Kim HJ, Jung JY, Kim JH, Kim HY, Kwon JH, Hwang SW, Park SR, Park CH, Kim KO, Kim MJ and Jang KM: Phase II study with oxaliplatin and S-1 for patients with metastatic colorectal cancer. Annals of Oncology *20(5)*: 892-896, 2009.

12 Yamada Y, Tahara M, Miya T, Satoh T, Shirao K, Shimada Y, Ohtsu A, Sasaki Y and Tanigawara Y: Phase I/II study of oxaliplatin with oral S-1 as first-line therapy for patients with metastatic colorectal cancer. Br J Cancer *98(6)*: 1034-1038, 2008.

13 Park YS, Hong YS, , Lim HY, Lee J, Kim TW, Kim KP, Kim SY, Baek JY, Kim JH, Lee KW, Chung IJ, Cho SH, Lee KH, Shin SJ, Kang HJ, Shin DB, Jo SJ and Lee JW: A randomized phase III study of SOX (S-1/oxaliplatin) *versus* COX (capecitabine/oxaliplatin) in patients with advanced colorectal cancer. J Clin Oncol 29 (Suppl; abstr 3524), 2011.

14 Hurwitz H, Fehrenbacher L, Novotny W, Cartwright T, Hainsworth J, Heim W, Berlin J, Baron A, Griffing S, Holmgren E, Ferrara N, Fyfe G, Rogers B, Ross R and Kabbinavar F: Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med *350(23)*: 2335-2342, 2004.

15 Cassidy J, Clarke S, Díaz-Rubio E, Scheithauer W, Figer A, Wong R, Koski S, Lichinitser M, Yang TS, Rivera F, Couture F, Sirzén F and Saltz L: 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, 2008.

16 Saltz LB, Clarke S, Díaz-Rubio E, Scheithauer W, Figer A, Wong R, Koski S, Lichinitser M, Yang TS, Rivera F, Couture F, Sirzén F and Cassidy J: 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, 2008.

17 Wong R, Cunningham D, Barbachano Y, Saffery C, Valle J, Hickish T, Mudan S, Brown G, Khan A, Wotherspoon A, Strimpakos AS, Thomas J, Compton S, Chua YJ and Chau I: A multicentre study of capecitabine, oxaliplatin plus bevacizumab as perioperative treatment of patients with poor-risk colorectal liver-only metastases not selected for upfront resection. Ann Oncol *22*: 2042-2048, 2011.

18 Beppu T, Emi Y, Tokunaga S, Oki E, Shirabe K, Ueno S, Kuramoto M, Kabashima A, Takahashi I, Samura H, Eguchi S, Akagi Y, Natsugoe S, Ogata Y, Kakeji Y, Baba H, Maehara Y; Kyushu Study group of Clinical Cancer (KSCC): Liver resectability of advanced liver-limited colorectal liver metastases following mFOLFOX6 with Bevacizumab (KSCC0802 Study). Anticancer Res *34*: 6655-6662, 2014.

19 Gruenberger T, Bridgewater J, Chau I, García Alfonso P, Rivoire M, Mudan S, Lasserre S, Hermann F, Waterkamp D and Adam R: Bevacizumab plus mFOLFOX-6 or FOLFOXIRI in patients with initially unresectable liver metastases from colorectal cancer: the OLIVIA multinational randomised phase II trial. Annals of Oncology *26*: 702-708, 2015.

20 Takahashi T, Shibata Y, Tojima Y, Tsuboi K, Sakamoto E, Kunieda K, Matsuoka H, Suzumura K, Sato M, Naganuma T, Sakamoto J, Morita S and Kondo K: Multicenter phase II study of modified FOLFOX6 as neoadjuvant chemotherapy for patients with unresectable liver-only metastases from colorectal cancer in Japan: ROOF study. Int J Clin Oncol *18*: 335-342, 2013.

21 Komatsu Y, Yuki S, Sogabe S, Fukushima H, Nakatsumi H, Kobayashi Y, Iwanaga I, Nakamura M, Hatanaka K, Miyagishima T, Kudo M, Munakata M, Meguro T, Tateyama M and Sakata Y: Phase II study of combined chemotherapy with irinotecan and S-1 (IRIS) plus bevacizumab in patients with inoperable recurrent or advanced colorectal cancer. Acta oncologica (Stockholm, Sweden) *51(7)*: 867-872, 2012.

22 Yamada Y, Yamaguchi T, Matsumoto H, Ichikawa Y, Goto A, Kato K, Hamaguchi T and Shimada Y: Phase II study of oral S-1 with irinotecan and bevacizumab (SIRB) as first-line therapy for patients with metastatic colorectal cancer. Invest New Drugs *30(4)*: 1690-1696, 2012.

23 Kato S, Andoh H, Gamoh M, Yamaguchi T, Murakawa Y, Shimodaira H, Takahashi S, Mori T, Ohori H, Maeda S, Suzuki T, Kato S, Akiyama S, Sasaki Y, Yoshioka T, Ishioka C; Tohoku Clinical Oncology Research and Education: Safety verification trials of mFOLFIRI and sequential IRIS + bevacizumab as first- or second-line therapies for metastatic colorectal cancer in Japanese patients. Oncology *83(2)*: 101-107, 2012.

24 Oki E, Emi Y, Miyamoto Y, Kabashima A, Higashi H, Ogata Y, Ikebe M, Saeki H, Tokunaga S, Shirabe K, Beppu T, Uchida S, Takatsuki M, Sakoda M, Eguchi S, Akagi Y, Kakeji Y, Baba H, Natsugoe S, Maehara Y; Kyushu Study Group of Clinical Cancer (KSCC): 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 Sep 3, 2015.

25 Twelves C, Wong A, Nowacki MP, Abt M, Burris H, Carrato A, Cassidy J, Cervantes A, Fagerberg J, Georgoulias V, Husseini F, Jodrell D, Koralewski P, Kroning H, Maroun J, Marschner N, McKendrick J, Pawlicki M, Rosso R, Schuller J, Seitz JF, Stabuc B, Tujakowski J, Van Hazel G, Zaluski J and Scheithauer W: Capecitabine as adjuvant treatment for stage III colon cancer. N Engl J Med *352(26)*: 2696-2704, 2005.

26 Cassidy J, Clarke S, Diaz-Rubio E, Scheithauer W, Figer A, Wong R, Koski S, Lichinitser M, Yang TS, Rivera F, Couture F, Sirzen F and Saltz L: 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, 2008.

27 Nanba D, Toki F, Barrandon Y and Higashiyama S: Recent advances in the epidermal growth factor receptor/ligand system biology on skin homeostasis and keratinocyte stem cell regulation. J Dermatol Sci *72*: 81-86, 2013.

28 Pastore S, Lulli D and Girolomoni G: Epidermal growth factor receptor signaling in keratinocyte biology: implications for skin toxicity of tyrosine kinase inhibitors. Arch Toxicol *88*: 1189-1203, 2014.

29 Maughan TS, Adams RA, Smith CG, Meade AM, Seymour MT, Wilson RH, Idziaszczyk S, Harris R, Fisher D, Kenny SL, Kay E, Mitchell JK, Madi A, Jasani B, James MD, Bridgewater J, Kennedy MJ, Claes B, Lambrechts D, Kaplan R, Cheadle JP;

MRC COIN Trial Investigators: Addition of cetuximab to oxaliplatin-based first-line combination chemotherapy for treatment of advanced colorectal cancer: results of the randomised phase 3 MRC COIN trials. Lancet *377*: 2103-2114, 2011.

30 Adams RA, Meade AM, Madi A, Fisher D, Kay E, Kenny S, Kaplan RS and Maughan TS: Toxicity associated with combination oxaliplatin plus fluoropyrimidine with or without cetuximab in the MRC COIN trial experience. Br J Cancer *100*: 251–258, 2009.

31 Hong YS, Park YS, Lim HY, Lee J, Kim TW, Kim KP, Kim SY, Baek JY, Kim JH, Lee KW, Chung IJ, Cho SH, Lee KH, Shin SJ, Kang HJ, Shin DB, Jo SJ and Lee JW: 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*: 1125-1132, 2012.

32 Feng QY, Wei Y, Chen JW, Chang WJ, Ye LC, Zhu DX and Xu JM: Anti-EGFR and anti-VEGF agents: important targeted therapies of colorectal liver metastases. World J Gastroenterol *20*: 4263-4275, 2014.

33 De Roock W, Piessevaux H, De Schutter J, Janssens M, De Hertogh G, Personeni N, Biesmans B, Van Laethem JL, Peeters M, Humblet Y, Van Cutsem E and Tejpar S: KRAS wild-type state predicts survival and is associated to early radiological response in metastatic colorectal cancer treated with cetuximab. Ann Oncol *19*: 508-515, 2008.

34 Piessevaux H, Buyse M, Schlichting M, Van Cutsem E, Bokemeyer C, Heeger S and Tejpar S: Use of early tumor shrinkage to predict long-term outcome in metastatic colorectal cancer treated with Cetuximab. J Clin Oncol *31(30)*: 3764-3775, 2013.

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