reported (5-7). Thus, the risks for the occurrence of adverse events should be assessed. BRiTE, a prospective, observational cohort study of BV-based chemotherapy for mCRC, showed the possible risk factors for GI perforation and ATE: age above 65 years, intact primary tumors, and prior adjuvant radiotherapy were related to GI perforation, and performance status greater than 1, hypertension, and past history of arterial disease were related to ATE (9).

Little information regarding the effects and adverse events of BV-containing chemotherapies in Japanese mCRC patients is available, because few prospective, large-scale, clinical studies using BV-containing regimens for mCRC have been performed in Japan. Therefore, predictive factors of BV-related adverse events and precise guidelines for administration of BV to Japanese mCRC patients are not well-established. In order to clarify the relationship between predictive factors and adverse events of BV-containing chemotherapy in Japanese patients, patients' background characteristics and frequencies of adverse events with systemic chemotherapy for mCRC were retrospectively investigated.

Patients and Methods

Patients. The present study retrospectively investigated 178 patients with unresectable, recurrent, or metastatic colorectal adenocarcinoma who started systemic chemotherapy during the period from June 11, 2007 to August 31, 2008 in three Institutions: the Department of Hematology and Oncology of Kyushu University Hospital, the Gastrointestinal and Medical Oncology Division of National Kyushu Cancer Center, and the Department of Medical Oncology in Hamanomachi Hospital, Fukuoka, Japan. Patients who were administered BV prior to this period were excluded.

Information of all cases was obtained from the participating Hospitals' medical records. Patients' background characteristics included age, sex, Eastern Cooperative Oncology Group (ECOG) performance status (PS), primary site of the tumor, and possible risk factors for serious adverse events of BV including remaining primary tumor, current bleeding, past and present history of arterial thromboembolism (ATE), hypertension, and proteinuria. In patients who were treated with BV-containing regimens during this survey period (BV group), chemotherapy regimens and their duration, best therapeutic effects, adverse events, and reasons for withdrawal of BV administration were investigated. In patients who were treated with chemotherapy without BV (CT group), the reasons for the primary decision to not use BV-containing regimens when chemotherapy was started were examined. Adverse events that occurred in the CT group were also observed in the above period. The present study was carried out according to the regulations of local Ethics committee in each Hospital and the Declaration of Helsinki.

Treatment. Patients received fluoropyrimidine-based chemotherapy with or without BV until disease progression, occurrence of intolerable adverse events, or patient's refusal. The combined chemotherapy regimens were selected by the physicians with the patients' consent. The dose of BV was 5 mg/kg or 10 mg/kg every 2 weeks. BV was administered intravenously in 100 ml of saline for 30-90 min. In cases of adverse events, the BV dose was not reduced, but administration of BV was suspended until recovery from the adverse events.

Assessments. At every bi-weekly visit, patients were assessed for adverse events by physical examination, urinalysis, blood cell counts, and serum chemistry. All adverse events were evaluated according to the Common Terminology Criteria for Adverse Events (CTC-AE) version 3.0. The most severe grades of adverse events during chemotherapy were recorded.

Statistics. Analyses of correlations between the occurrence of BV-specific adverse events and their possible risk factors were performed using the Fisher's exact test.

Results

Patients' background characteristics and treatments. Overall, 87 of 178 patients were treated with BV-containing chemotherapy (BV group) during the observation period, and 91 patients were treated with non-BV-containing chemotherapy (CT group). No significant differences in sex, age, and primary site were identified between the two groups (Table I). Patients who had primary tumors tended to be treated with chemotherapy without BV. Bleeding risks were significantly more frequently observed in the CT group. No significant differences between the two patient groups were observed in the other factors.

In the BV group, BV-containing regimens were used in the first (17%), second (35%), and third line (29%) of chemotherapy (Table II). Combined chemotherapy regimens were oxaliplatin-based FOLFOX (48%) and irinotecan-based FOLFIRI or IFL (44%). The median number of BV administrations was 7, and the median duration of BV-containing chemotherapy was 8.1 months. In 71 regimens of BV-containing chemotherapy in which the therapeutic effect was confirmed until August 31, 2008, the response rate and the disease control rate were 18% and 78% in all lines of treatment, respectively, and 27% and 82% in first-line treatment, respectively (Table III). There were 15 patients who were treated with two BV-containing chemotherapy regimens. In 10 of these 15 patients, BV was administered after disease progression in their prior chemotherapy with BV. The other 5 patients stopped chemotherapy because of oxaliplatin-induced allergies (3 patients), diarrhea (1 patient), and patient's refusal (1 patient), but BV was continued for the subsequent chemotherapies including irinotecan-based or oxaliplatin-based regimens, which were not used in the prior therapy. The confirmed responses of the second BV-containing chemotherapy in 5 patients were 3 stable diseases and 2 progressive diseases.

Safety. Therapy-related toxicities in the BV group were assessed according to the Common Terminology Criteria of Adverse Events version 3.0 (CTC-AE ver.3.0) (Table IV). In

Table I. *Baseline characteristics of all patients.*

Characteristic	BV-containing Regimen (BV group) No.	%	Non-BV-containing regimen (CT group) No.	%	*p*-Value
Gender					
Male	47	54	44	48	0.45
Female	40	46	47	52	
Age					
Median (range), year	63 (36-82)		65 (21-84)		0.76
74 and younger	76	86	74	81	0.31
75 and older	11	14	17	19	
Primary tumor					
Colon	45	52	51	56	0.65
Rectum	42	48	40	44	
Resected	69	78	60	66	0.06
Remaining	18	22	31	34	
Bleeding risk					
None	85	98	75	82	< 0.01
Any risk	2	2	16	18	
Primary tumor	0		9		
Invading tumor	1		3		
Genital organ	1		2		
Surgical wound	0		1		
Thrombocytopenia	0		1		
Thromboembolic risk					
None	81	93	79	87	0.22
Any risk	6	7	11	13	
Cerebral infarction	4		4		
ASO	1		2		
Ischemic heart disease	1		1		
Severe Arteriosclerosis	0		2		
Atrial fibrillation	0		1		
DIC	0		1		
Blood pressure					
Normotension	73	84	70	77	0.26
Hypertension	14	16	21	23	
Proteinuria					
Negative	80	92	82	90	0.80
Positive	7	8	9	10	

BV; Bevacizumab, ASO; arteriosclerosis obliterans, DIC; disseminated intravascular coagulation.

Table II. *Characteristics of the systemic chemotherapy regimens of the BV group.*

Characteristics	Number of patients	%
Regimen	102	(Total)
FOLFOX	49	48
FOLFIRI/IFL	45	44
S-1 + Irinotecan	4	4
5-FU + LV	4	4
Administration of BV		
median (range)	7	(1-28)
Treatment with BV		
Continuation	48	55
Cessation	39	45
Duration of therapy		
median in months (range)	8.1	(0.5-14.0)
Treatment line		
1st	17	17
2nd	36	35
3rd	30	29
4th or later	19	19

FOLFOX; 5-FU/leucovorin plus oxaliplatin, FOLFIRI/IFL; 5-FU/leucovorin plus irinotecan, LV; leucovorin.

Table III. *Efficacy of chemotherapy in the BV group.*

Treatment line	Response CR	PR	SD	PD	NE	RR (%)	DCR (%)
1st	0	3	6	1	1	27	82
2nd	0	5	14	5	1	20	76
3rd	0	4	14	6	0	17	75
4th or later	0	1	10	2	0	8	85
All	0	13	44	14	2	18	78

RR; Response rate, DCR; disease control rate.

terms of hematological toxicities, neutropenia was observed in 87% of patients (grade 3/4; 41%), anemia in 79% (grade 3/4; 5%) and thrombocytopenia in 17% (grade 3/4; 2%). Febrile neutropenia occurred in 8%. Concerning non-hematological toxicities, general fatigue was observed in 71%, anorexia in 76%, nausea and vomiting in 61%, and peripheral neuropathy in 64%. All grades of diarrhea occurred in 54% of patients, and more than grade 3 was seen in 5%. In BV-related toxicities, bleeding was observed in 23% of patients (10 cases of nasal bleeding, 1 case of gingival bleeding, 9 cases of gastrointestinal bleeding), hypertension in 22%, proteinuria in 15%, and delayed wound healing in 4%. There were no treatment-related deaths.

Risk factors for BV-related adverse events. The relationships between BV-related adverse events and possible risk factors were analyzed. Gastrointestinal perforation did not occur in patients with or without primary tumor lesions. As mentioned above, 9 patients had gastrointestinal bleeding, including 4 with melena, 4 with bleeding from the stoma, and 1 proctorrhagia, and no correlation was observed between remaining primary tumors and bleeding (Table V). No arterial thrombosis events occurred in the patients with or without a present or past history of thrombotic events. On the other hand, patients with hypertension before starting

Table IV. *Adverse events in the BV group.*

Adverse event	Grade (CTC-AE ver 3.0) 1	2	3	4	Total (%)	Grade 3/4 (%)
Neutropenia	22	18	24	12	87	41
Anemia	44	21	4	0	79	5
Thrombocytopenia	9	4	1	1	17	2
Febrile Neutropenia	-	-	6	1	8	8
Fatigue	42	19	1	0	71	1
Anorexia	46	19	1	0	76	1
Nausea/vomiting	42	10	1	0	61	1
Stomatitis	14	3	2	0	22	2
Diarrhea	35	8	3	1	54	5
Stomach ache	11	1	1	0	15	1
Peripheral neuropathy	31	18	7	0	64	8
Allergy	5	3	1	0	10	1
Nasal/gingival bleeding	11	0	0	0	11	0

Table V. *BV-containing regimen-related gastrointestinal bleeding in patients with or without primary tumor.*

Primary tumor	Gastrointestinal bleedings		
	No	Yes*	*p*-Value
Resected	63	6	0.39
Remained	15	3	

*These 9 cases with gastrointestinal bleedings include 4 melenas, 4 bleedings of stoma and 1 proctorrhagia.

BV-containing chemotherapy had significant deterioration of hypertension (p=0.02) (Table VI). Therapy-related deterioration of proteinuria was not correlated with presence of proteinuria before chemotherapy (Table VII).

Forty-eight patients in the BV group continued to the end of this surveillance period in August 2008, and 39 patients had stopped BV-containing chemotherapy because of progressive disease (20 patients) and toxicity (11 patients).

Reasons for non-BV chemotherapy in the CT group. The reasons why BV was not administered in the CT group were also determined (Table VIII). The most frequent reason for this was the risk of bleeding (11 patients, 12%); in detail, 5 patients in the CT group had active bleeding from the primary site, 3 had bleeding from sites of tumor invasion, and 2 had bleeding from invasion of genital organs and other sites. Eleven patients (12%) were not administered BV because due to patients' refusal. BV was not used in 10 patients with a current or past history of arterial thrombotic events and in 8 patients with severe peritoneal dissemination.

Table VI. *BV-containing regimen-related hypertension in patients with or without hypertension before therapy.*

Blood pressure before therapy	BP grade (CTC-AE v3.0) 0	1	2	3	4	*p*-Value
Normotension	60	8	5	0	0	0.02
Hypertension	8	1	4	1	0	

Since 7 patients had surgery immediately prior to chemotherapy, the use of BV was reduced.

Discussion

BV has been widely used in systemic chemotherapy for mCRC. Various large-scale, phase III clinical studies, mainly conducted in Western countries, have shown the efficacy and safety profiles of BV-containing chemotherapy regimens (5-8). Tamiya *et al.* (10) reported on a retrospective review of adverse events in 65 Japanese patients with mCRC treated with BV-containing regimens and showed similar safety profiles to those of previous prospective trials. Although these reports encouraged the use of BV as one of the standard chemotherapeutic agents for mCRC, selection of patients who could be safely treated with BV-containing therapy is required in the clinical setting. It is, thus, important to identify the risk factors for predicting adverse events specifically caused by BV in Japanese patients.

The present study analyzed clinical data from patients with mCRC who had been treated with systemic chemotherapy during the period of 15 months from the approval of BV in Japan. The efficacy and safety of BV-containing chemotherapies and the possible risk factors related to BV-specific adverse events were identified. Since it had been known that bleeding occurred in around 3% of patients with BV-containing chemotherapies (5-8), mCRC patients with possible bleeding risks were excluded from BV administration in the CT group. Two patients, one with a history of hemorrhage from a gynecological organ and another with a remaining primary tumor, were treated with a BV-containing regimen and had no bleeding episodes during the treatment period. The significant risk factors for bleeding could not be identified because no hemorrhagic events occurred in either the BV group or the CT group. These facts suggested that active bleeding or highly hemorrhagic lesions might be appropriate risk factors for BV-related severe bleeding, and avoidance of BV administration in this population might be appropriate. It may be important to assess the bleeding risk in advance to prevent severe bleeding, and BV might be administered safely to patients with a low bleeding risk.

Table VII. *BV-containing regimen-related deterioration of proteinuria in patients with proteinuria before therapy.*

Proteinuria before therapy (CTC-AE v3.0)	Proteinuria grade (Number of patients)					Deterioration (Number of patients)		*p*-Value
	0	1	2	3	4	No	Yes	
0	73	6	1	0	0	73	7	0.15
1	1	2	2	0	0	3	2	
2	0	0	2	0	0	2	0	

The incidence of arterial thrombosis has been reported to be 1.7% in a cytotoxic chemotherapy-alone group and 3.8% in a BV-containing chemotherapy group, in a meta-analysis including clinical trials for mCRC, non-small cell lung cancer, and breast cancer (11). The multivariate analysis revealed that age over 65 years (p=0.01) and a history of arterial thrombosis (p<0.001) were independent risk factors for ATE (11). In the present study, BV was not given to 10 patients with any risk of thrombosis. Given the risk factors demonstrated in the previous report, 339 cases were >65 years of age, and 89 cases had a history of thrombosis. In contrast, 6 patients who had had possible risks for thrombosis, such as a history of brain infarction in 4 patients, arteriosclerosis obliterans in 1, and ischemic heart disease in 1, were successfully treated in the present study. Importantly, the disease activities of thrombosis in all 6 patients were diagnosed as minimal prior to chemotherapy, and no severe thrombotic events occurred in these patients. Establishment of precise criteria for administering BV in patients with a history of thrombotic events is also required.

In the present study, hypertension prior to BV-containing therapy was identified as a significant risk factor for the induction of worse hypertension by BV. On the other hand, in the BRiTE study, *de novo* hypertension appeared in 22% of BV-treated patients without baseline hypertension, and deterioration of hypertension in BV-treated patients with baseline hypertension was similarly observed in 22% (9). Ethnic differences might explain for the difference between present findings and those of the previous study. It has been reported that the sensitivity to sodium differs between Asians and Caucasians or Africans, suggesting that molecular mechanisms of BV-induced hypertension may differ among races (12).

Identification of risk factors has two roles: prevention of severe toxicities induced by chemotherapy, and avoidance of losing the chance for patients to be treated with appropriate chemotherapy. Because patients harboring possible risks were often excluded from enrollment in clinical trials, prospective trials focusing on that population might be important. In addition, retrospective analysis might be helpful to reveal the safety and effectiveness of BV in such patient populations. The present study demonstrated that BV-containing therapy in Japanese mCRC patients showed a similar toxicity profile to the one previously reported. It was suggested that suitable assessment of possible risk factors could lead to safe treatment with BV. Since Japanese mCRC patients with hypertension had a higher possibility of worse hypertension with BV, careful follow-up is needed.

Table VIII. *Reasons for choosing non-BV chemotherapy.*

Reason	No.	%
Remained primary site	4	4
Bleeding risk at	11	12
Primary site	5	
Invaded site of tumor	3	
Genital organs	2	
Thrombocytopenia	1	
Thromboembolic risk	10	11
Cerebral infarction	4	
Severe arteriosclerosis	2	
Atrial fibrillation	1	
Ischemic heart disease	1	
Thrombocytosis	1	
DIC*	1	
Hypertension	1	1
Patient's refusal	11	12
Severe peritoneal dissemination	8	9
Immediately prior to operation	7	8
Doctor's decision	7	8
Poor performance status	5	5
Advanced age	4	4
Combined radiotherapy	3	3
Preceding operation	2	2
Changing hospital	1	1
Others	8	9
Double cancers	2	
Diabetes mellitus	2	
Aftereffect of prior therapy	2	
Neuroendcrine component	1	
Renal dysfunction	1	

*Disseminated intravascular coagulation.

Acknowledgements

The Authors would like to thank Dr. Risa Tanaka for providing patient data. The Authors would also like to thank the medical staff of each institution who contributed to treatment of the patients.

References

1 Presta LG, Chen H, O'Connor SJ, Chisholm V, Meng YG, Krummen L, Winkler M and Ferrara N: Humanization of an anti-vascular endothelial growth factor monoclonal antibody for the therapy of solid tumors and other disorders. Cancer Res *57*: 4593-4599, 1997.

2 McCrudden KW, Hopkins B, Frischer J, Novikov A, Huang J, Kadenhe A, New T, Yokoi A, Yamashiro DJ, Kandel JJ and Middlesworth W: Anti-VEGF antibody in experimental hepatoblastoma: suppression of tumor growth and altered angiogenesis. J Pediatr Surg *38*: 308-314, 2003.

3 Yuan F, Chen Y, Dellian M, Safabakhsh N, Ferrara N and Jain RK: Time-dependent vascular regression and permeability changes in established human tumor xenografts induced by an anti-vascular endothelial growth factor/vascular permeability factor antibody. Proc Natl Acad Sci USA *93*: 14765-14770, 1996.

4 Willett CG, Boucher Y, di Tomaso E, Duda DG, Munn LL, Tong RT, Chung DC, Sahani DV, Kalva SP, Kozin SV, Mino M, Cohen KS, Scadden DT, Hartford AC, Fischman AJ, Clark JW, Ryan DP, Zhu AX, Blaszkowsky LS, Chen HX, Shellito PC, Lauwers GY and Jain RK: Direct evidence that the VEGF-specific antibody BV has antivascular effects in human rectal cancer. Nat Med *10*: 145-147, 2004.

5 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: BV plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med *350*: 2335-2342, 2004.

6 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: BV in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer: a randomized phase III study. J Clin Oncol *26*: 2013-2019, 2008.

7 Giantonio BJ, Catalano PJ, Meropol NJ, O'Dwyer PJ, Mitchell EP, Alberts SR, Schwartz MA, Benson AB 3rd and Eastern Cooperative Oncology Group Study E3200: BV in combination with oxaliplatin, fluorouracil, and leucovorin (FOLFOX4) for previously treated metastatic colorectal cancer: results from the Eastern Cooperative Oncology Group Study E3200. J Clin Oncol *25*: 1539-1544, 2007.

8 Bennouna J, Sastre J, Arnold D, Österlund P, Greil R, von Cutsem E, von Moos R, Viéitez JM, Bouché O, Borg C, Steffens CC, Alonso-Orduña V, Schlichting C, Reyes-Rivera I, Bendahmane B, André T, Kubicka S, on behalf of the ML18147 Study Investigators: Continuation of BV after first progression in metastatic colorectal cancer (ML18147): a randomised phase 3 trial. Lancet Oncol *14*: 29-37, 2013.

9 Kozloff M, Yood MU, Berlin J, Flynn PJ, Kabbinavar FF, Purdie DM, Ashby MA, Dong W, Sugrue MM, Grothey A; Investigators of the BRiTE study: Clinical outcomes associated with bevacizumab-containing treatment of metastatic colorectal cancer: the BRiTE observational cohort study. Oncologist *14*: 862-870, 2009.

10 Tamiya A, Yamazaki K, Boku N, Machida N, Kojima T, Taku K, Yasui H, Fukutomi A, Hironaka S and Onozawa Y: Safety of BV treatment in combination with standard chemotherapy for metastatic colorectal cancer: a retrospective review of 65 Japanese patients. Int J Clin Oncol *14*: 513-517, 2009.

11 Scappaticci FA, Skillings JR, Holden SN, Gerber HP, Miller K, Kabbinavar F, Bergsland E, Ngai J, Holmgren E, Wang J and Hurwitz H: Arterial thromboembolic events in patients with metastatic carcinoma treated with chemotherapy and BV. J Natl Cancer Inst *99*: 1232-1239, 2007.

12 International Consortium for Blood Pressure Genome-Wide Association Studies: Genetic variants in novel pathways influence blood pressure and cardiovascular disease risk. Nature *478*: 103-109, 2011.

Received January 5, 2014
Revised January 15, 2014
Accepted January 17, 2014

Instructions to Authors 2014

General Policy. ANTICANCER RESEARCH (AR) will accept original high quality works and reviews on all aspects of experimental and clinical cancer research. The Editorial Policy suggests that priority will be given to papers advancing the understanding of cancer causation, and to papers applying the results of basic research to cancer diagnosis, prognosis, and therapy. AR will also accept the following for publication: (a) Abstracts and Proceedings of scientific meetings on cancer, following consideration and approval by the Editorial Board; (b) Announcements of meetings related to cancer research; (c) Short reviews (of approximately 120 words) and announcements of newly received books and journals related to cancer, and (d) Announcements of awards and prizes.

The principal aim of AR is to provide prompt publication (print and online) for original works of high quality, generally within 1-2 months from final acceptance. Manuscripts will be accepted on the understanding that they report original unpublished works on the cancer problem that are not under consideration for publication by another journal, and that they will not be published again in the same form. All authors should sign a submission letter confirming the approval of their article contents. All material submitted to AR will be subject to review, when appropriate, by two members of the Editorial Board and by one suitable outside referee. The Editors reserve the right to improve manuscripts on grammar and style.

The Editors and Publishers of AR accept no responsibility for the contents and opinions expressed by the contributors. Authors should warrantee due diligence in the creation and issuance of their work.

NIH Open Access Policy. The journal acknowledges that authors of NIH funded research retain the right to provide a copy of the final manuscript to the NIH four months after publication in ANTICANCER RESEARCH, for public archiving in PubMed Central.

Copyright. Once a manuscript has been published in ANTICANCER RESEARCH, which is a copyrighted publication, the legal ownership of all published parts of the paper has been transferred from the Author(s) to the journal. Material published in the journal may not be reproduced or published elsewhere without the written consent of the Managing Editor or Publisher.

Format. Two types of papers may be submitted: (i) Full papers containing completed original work, and (ii) review articles concerning fields of recognisable progress. Papers should contain all essential data in order to make the presentation clear. Reasonable economy should be exercised with respect to the number of tables and illustrations used. Papers should be written in clear, concise English. Spelling should follow that given in the "Shorter Oxford English Dictionary".

Manuscripts. Submitted manuscripts should not exceed fourteen (14) pages (approximately 250 words per double - spaced typed page), including abstract, text, tables, figures, and references (corresponding to 4 printed pages). Papers exceeding four printed pages will be subject to excess page charges. All manuscripts should be divided into the following sections:
(a) *First page* including the title of the presented work [not exceeding fifteen (15) words], full names and full postal addresses of all Authors, name of the Author to whom proofs are to be sent, key words, an abbreviated running title, an indication "review", "clinical", "epidemiological", or "experimental" study, and the date of submission. (Note: The order of the Authors is not necessarily indicative of their contribution to the work. Authors may note their individual contribution(s) in the appropriate section(s) of the presented work); (b) *Abstract* not exceeding 150 words, organized according to the following headings: Background/Aim - Materials and Methods/Patients and Methods - Results - Conclusion; (c) *Introduction;* (d) *Materials and Methods/Patients and Methods;* (e) *Results;* (f) *Discussion;* (g) *Acknowledgements;* (h) *References.* All pages must be numbered consecutively. Footnotes should be avoided. Review articles may follow a different style according to the subject matter and the Author's opinion. Review articles should not exceed 35 pages (approximately 250 words per double-spaced typed page) including all tables, figures, and references.

Figures. All figures (whether photographs or graphs) should be clear, high contrast, at the size they are to appear in the journal: 8.00 cm (3.15 in.) wide for a single column; 17.00 cm (6.70 in.) for a double column; maximum height: 20.00 cm (7.87 in.). Graphs must be submitted as photographs made from drawings and must not require any artwork, typesetting, or size modifications. Symbols, numbering and lettering should be clearly legible. The number and top of each figure must be indicated. Colour plates are charged.

Tables. Tables should be typed double-spaced on a separate page, numbered with Roman numerals and should include a short title.

References. Authors must assume responsibility for the accuracy of the references used. Citations for the reference sections of submitted works should follow the standard form of "Index Medicus" and must be numbered consecutively. In the text, references should be cited by number. Examples: 1 Sumner AT: The nature of chromosome bands and their significance for cancer research. Anticancer Res 1: 205-216, 1981. 2 McGuire WL and Chamnes GC: Studies on the oestrogen receptor in breast cancer. In: Receptors for Reproductive Hormones (O' Malley BW, Chamnes GC (eds.). New York, Plenum Publ Corp., pp 113-136, 1973.

Nomenclature and Abbreviations. Nomenclature should follow that given in "Chemical Abstracts", "Index Medicus", "Merck Index", "IUPAC –IUB", "Bergey's Manual of Determinative Bacteriology", The CBE Manual for Authors, Editors and Publishers (6th edition, 1994), and MIAME Standard for Microarray Data. Human gene symbols may be obtained from the HUGO Gene Nomenclature Committee (HGNC) (http://www.gene.ucl.ac.uk/). Approved mouse nomenclature may be obtained from http://www.informatics.jax.org/. Standard abbreviations are preferable. If a new abbreviation is used, it must be defined on first usage.

Clinical Trials. Authors of manuscripts describing clinical trials should provide the appropriate clinical trial number in the correct format in the text.
For International Standard Randomised Controlled Trials (ISRCTN) Registry (a not-for-profit organization whose registry is administered by Current Controlled Trials Ltd.) the unique number must be provided in this format: ISRCTNXXXXXXXX (where XXXXXXXX represents the unique number, always prefixed by "ISRCTN"). Please note that there is no space between the prefix "ISRCTN" and the number. Example: ISRCTN47956475.

For Clinicaltrials.gov registered trials, the unique number must be provided in this format: NCTXXXXXXXX (where XXXXXXXX represents the unique number, always prefixed by 'NCT'). Please note that there is no space between the prefix 'NCT' and the number. Example: NCT00001789.

Ethical Policies and Standards. ANTICANCER RESEARCH agrees with and follows the "Uniform Requirements for Manuscripts Submitted to Biomedical Journals" established by the International Committee of Medical Journal Editors in 1978 and updated in October 2001 (www.icmje.org). Microarray data analysis should comply with the "Minimum Information About Microarray Experiments (MIAME) standard". Specific guidelines are provided at the "Microarray Gene Expression Data Society" (MGED) website. Presentation of genome sequences should follow the guidelines of the NHGRI Policy on Release of Human Genomic Sequence Data. Research involving human beings must adhere to the principles of the Declaration of Helsinki and Title 45, U.S. Code of Federal Regulations, Part 46, Protection of Human Subjects, effective December 13, 2001. Research involving animals must adhere to the Guiding Principles in the Care and Use of Animals approved by the Council of the American Physiological Society. The use of animals in biomedical research should be under the careful supervision of a person adequately trained in this field and the animals must be treated humanely at all times. Research involving the use of human foetuses, foetal tissue, embryos and embryonic cells should adhere to the U.S. Public Law 103-41, effective December 13, 2001.

Submission of Manuscripts. Please follow the Instructions to Authors regarding the format of your manuscript and references. There are 3 ways to submit your article (NOTE: Please use only one of the 3 options. Do not send your article twice.):

1. To submit your article online please visit: IIAR-Submissions (http://www.iiar-anticancer.org/submissions/login.php)
2. You can send your article via e-mail to journals@iiar-anticancer.org. Please remember to always indicate the name of the journal you wish to submit your paper. The text should be sent as a Word document (*doc) attachment. Tables, figures and cover letter can also be sent as e-mail attachments.
3. You can send the manuscript of your article via regular mail in a USB stick, DVD, CD or floppy disk (including text, tables and figures) together with three hard copies to the following address:
   John G. Delinasios
   International Institute of Anticancer Research (IIAR)
   Editorial Office of ANTICANCER RESEARCH,
   IN VIVO, CANCER GENOMICS and PROTEOMICS.
   1st km Kapandritiou-Kalamou Road
   P.O. Box 22, GR-19014 Kapandriti, Attiki
   GREECE

Submitted articles will not be returned to Authors upon rejection.

Galley Proofs. Unless otherwise indicated, galley proofs will be sent to the first-named Author of the submission. Corrections of galley proofs should be limited to typographical errors. Reprints, PDF files, and/or Open Access may be ordered after the acceptance of the paper. Requests should be addressed to the Editorial Office.

J Cancer Res Clin Oncol (2015) 141:153–160
DOI 10.1007/s00432-014-1783-3

ORIGINAL ARTICLE – CLINICAL ONCOLOGY

A phase 3 non-inferiority study of 5-FU/*l*-leucovorin/irinotecan (FOLFIRI) versus irinotecan/S-1 (IRIS) as second-line chemotherapy for metastatic colorectal cancer: updated results of the FIRIS study

Hirofumi Yasui · Kei Muro · Yasuhiro Shimada · Akihito Tsuji · Shinichi Sameshima · Hideo Baba · Taroh Satoh · Tadamichi Denda · Kenji Ina · Tomohiro Nishina · Kensei Yamaguchi · Taito Esaki · Shinya Tokunaga · Hiroyuki Kuwano · Narikazu Boku · Yoshito Komatsu · Masahiko Watanabe · Ichinosuke Hyodo · Satoshi Morita · Kenichi Sugihara

Received: 20 May 2014 / Accepted: 16 July 2014 / Published online: 9 August 2014

Abstract

Purpose The FIRIS study previously demonstrated non-inferiority of IRIS (irinotecan plus S-1) to FOLFIRI (5-fluorouracil/leucovorin with irinotecan) for progression-free survival as the second-line chemotherapy for metastatic colorectal cancer (mCRC) as the primary endpoint. The overall survival (OS) data were immature at the time of the primary analysis.

Methods Between 30 January 2006 and 29 January 2008, 426 patients with mCRC who failed in first-line chemotherapy were randomly assigned to receive either FOLFIRI or IRIS. After the primary analysis, the follow-up survey was cut off on 29 July 2010, and the final OS data were analysed.

Results With a median follow-up of 39.2 months, the median OS was 17.4 months in the FOLFIRI group and 17.8 months in the IRIS group [hazard ratio (HR) 0.900; 95 % confidence interval (CI) 0.728–1.112]. In the pre-planned subgroup of patients who received prior chemotherapy containing oxaliplatin, the median OS was

H. Yasui (✉)
Division of Gastrointestinal Oncology, Shizuoka Cancer Center, 1007 Shimonagakubo, Nagaizumi-cho, Sunto-gun, Shizuoka 411-8777, Japan
e-mail: h.yasui@scchr.jp

K. Muro
Department of Clinical Oncology, Aichi Cancer Center Hospital, Nagoya, Japan

Y. Shimada
Division of Gastrointestinal Oncology, National Cancer Center Hospital, Tokyo, Japan

A. Tsuji
Department of Medical Oncology, Kobe City Medical Center General Hospital, Kobe, Japan

S. Sameshima
Department of Surgery, Dokkyo Medical University Koshigaya Hospital, Koshigaya, Japan

H. Baba
Department of Gastroenterological Surgery, Graduate School of Medical Sciences, Kumamoto University, Kumamoto, Japan

T. Satoh
Department of Frontier Science for Cancer and Chemotherapy, Osaka University Graduate School of Medicine, Suita, Japan

T. Denda
Department of Gastroenterology, Chiba Cancer Center, Chiba, Japan

K. Ina
Department of Medical Oncology, Nagoya Memorial Hospital, Nagoya, Japan

T. Nishina
Department of Medical Oncology, National Hospital Organization Shikoku Cancer Center, Matsuyama, Japan

K. Yamaguchi
Department of Gastroenterology, Saitama Cancer Center, Ina-machi, Kitaadachi-gun, Saitama, Japan

T. Esaki
Department of Gastrointestinal and Medical Oncology, National Kyushu Cancer Center, Fukuoka, Japan

S. Tokunaga
Department of Clinical Oncology, Osaka City General Hospital, Osaka, Japan

H. Kuwano
Department of General Surgical Science, Graduate School of Medicine, Gunma University, Maebashi, Japan

12.7 months in the FOLFIRI group and 15.3 months in the IRIS group (HR 0.755; 95 % CI 0.580–0.983).
Conclusions IRIS is non-inferior to FOLFIRI for OS as second-line chemotherapy for mCRC. IRIS can be an option for second-line chemotherapy of mCRC. (ClinicalTrials.gov Number: NCT00284258).

Keywords Colorectal cancer · FIRIS · Irinotecan · IRIS · S-1

Introduction

At present, the combination of 5-fluorouracil (5-FU)/leucovorin (LV) with either oxaliplatin (FOLFOX) or irinotecan (FOLFIRI) is the mainstream chemotherapy for metastatic colorectal cancer (mCRC) worldwide (O'Neil and Goldberg 2008; National Comprehensive Cancer Network 2014a, b; Tournigand et al. 2004).

In Japan, FOLFOX or FOLFIRI is widely used as the first-line or second-line chemotherapy for mCRC. However, infusional 5-FU-based regimens such as FOLFOX or FOLFIRI are inconvenient because continuous infusion and implantation of an intravenous port system are required. In addition, their use is sometimes complicated by catheter-related infections and thrombosis. Replacement of infusional 5-FU with an oral anticancer drug may be convenient and reduce the burden on patients and healthcare professionals.

In Japan, oral S-1 has been widely used for the treatment of gastrointestinal cancers. In phase 2 studies of IRIS combining S-1 and irinotecan for mCRC, the response rates ranged from 52.5 to 62.5 %, and the median progression-free survival (PFS) was 7.8–8.6 months, suggesting that IRIS may have comparable efficacy to FOLFIRI as a first-line therapy (Goto et al. 2006; Komatsu et al. 2011; Tsunoda et al. 2009; Komatsu et al. 2010: Shiozawa et al. 2010).

The FIRIS study is a phase 3 randomised study to investigate the non-inferiority of IRIS to FOLFIRI, which is a standard second-line chemotherapy for mCRC after failure of fluoropyrimidine chemotherapy with or without oxaliplatin. In the primary analysis, the median PFS was 5.1 months in the FOLFIRI group and 5.8 months in the IRIS group [hazard ratio (HR) 1.077; 95 % confidence interval (CI) 0.879–1.319], demonstrating the non-inferiority of IRIS to FOLFIRI (Muro et al. 2010). Thereafter, in the ESMO Consensus Guidelines for management of patients with colon and rectal cancer, IRIS is listed in the table of the treatment options (Schmoll et al. 2012). However, the survival data of the FIRIS study were immature. In this paper, an updated analysis focusing on overall survival (OS) is reported.

Patients and methods

Study design and treatment

This randomised, open-label, phase 3 study of second-line chemotherapy for patients with mCRC was conducted at 40 institutions in Japan (see "Appendix"). The eligibility criteria and design were described in detail in a previous report (Muro et al. 2010).

The patients were centrally randomised to receive either FOLFIRI or IRIS using the minimisation method with stratification by institution, prior therapy (with oxaliplatin vs. without oxaliplatin), and performance status (PS; 0 vs. 1). In the FOLFIRI group, the patients received *l*-LV (200 mg/m^2) and irinotecan (150 mg/m^2) followed by a bolus injection of 5-FU (400 mg/m^2) on day 1, and then continuous infusion of 5-FU (2,400 mg/m^2) over 46 h, repeated every 2 weeks (4 weeks counted as one course). The dose of irinotecan (150 mg/m^2) given to the FOLFIRI group is the upper limit of the approved dose in Japan (Fuse et al. 2008). The IRIS group received irinotecan (125 mg/m^2) on days 1 and 15 and S-1 [40–60 mg/body, based on the body surface area (BSA): BSA < 1.25 m^2, 40 mg/body; 1.25 m^2 ≤ BSA < 1.5 m^2, 50 mg/body; BSA ≥ 1.5 m^2, 60 mg/body] twice daily for 2 weeks followed by 2 weeks of rest, based on the results of the phase 2 study (Goto et al. 2006). The treatment was continued until one of the following events occurred: disease progression (PD); unacceptable toxicity; or patient's refusal to continue treatment.

The primary objective of the study was to demonstrate the non-inferiority of IRIS to FOLFIRI for PFS.

N. Boku
Department of Clinical Oncology, St. Marianna University School of Medicine, Kawasaki, Japan

Y. Komatsu
Department of Cancer Chemotherapy, Hokkaido University Hospital Cancer Center, Sapporo, Japan

M. Watanabe
Department of Surgery, Kitasato University School of Medicine, Sagamihara, Japan

I. Hyodo
Division of Gastroenterology, Tsukuba University Hospital, Tsukuba, Japan

S. Morita
Department of Biostatistics and Epidemiology, Yokohama City University Medical Center, Yokohama, Japan

K. Sugihara
Department of Surgical Oncology, Tokyo Medical and Dental University Graduate School, Tokyo, Japan

The secondary endpoints included OS, response rate, and safety. In addition, pre-planned subgroup analyses were performed.

The protocol of the study was approved by the institutional review board or ethics committee and was conducted in compliance with the Declaration of Helsinki and Japanese ethical guideline for clinical studies. Written informed consent was obtained from all patients participating in the study.

Study assessments

Physical examinations and laboratory tests were performed at baseline and repeated at least every 2 weeks during the treatment. Tumours were assessed at baseline (within 1 month before enrolment), 2, 3, and 4 months after enrolment, and every 2 months thereafter until progression. Progression was defined when any of the following three events occurred: (1) PD based on the response evaluation criteria in solid tumours (RECIST) version 1.0; (2) clinical progression judged by the investigator; or (3) death from any cause without progression. PFS was calculated from the date of randomisation to the date of the events described above.

OS was calculated from the date of randomisation to the date of death from any cause. Surviving patients, including those lost to follow-up, were censored at the date of last confirmation of survival. Toxicity was evaluated based on the Common Terminology Criteria for Adverse Events version 3.0 (CTCAE v3.0).

Statistical analysis

The intent-to-treat (ITT) population consisted of all randomised patients, and the per-protocol set (PPS) population was defined as the ITT population excluding patients who violated protocols to a considerable extent, including major protocol inclusion/exclusion criteria or treatment protocols.

The primary endpoint of PFS was assumed to be 4 months in both groups. By defining a 1-month shorter PFS with IRIS than with FOLFIRI as the acceptance limit for non-inferiority, which was also the minimum difference detected by monthly image examinations, a non-inferiority margin of 1.333 was selected. After the required number of events was calculated with a one-sided α of 0.025 and a power of 80 %, a target sample size of 400 patients was selected.

For the primary endpoint of PFS and the secondary endpoint of OS, the HR for IRIS to FOLFIRI and its 95 % CI were calculated to show the non-inferiority of IRIS to FOLFIRI, respectively. Furthermore, Bayesian analyses were carried out to assess the robustness of these preliminary results. Post hoc analyses for posterior probabilities with log HR within the range of 1.333–1.15 (a stricter threshold) were performed (Spiegelhalter et al. 1994).

For the primary analysis, the collection of the primary endpoint PFS data was cut off on 31 December 2008 and the number of confirmed events was 389 (Muro et al. 2010). The final analysis was performed on 29 July 2010 (2.5 years after the last patient was enrolled, as pre-specified in the protocol).

Subgroup analyses were pre-planned to determine whether therapeutic efficacy interacted with sex, age, histological type, PS, and prior chemotherapy with or without oxaliplatin. PFS and OS were estimated using the Kaplan–Meier method. The 95 % CI for the median PFS and OS was calculated using the method of Brookmeyer and Crowley (Brookmeyer and Crowley 1982). All p values were two-sided. All statistical analyses were performed using SAS version 8.2 (SAS Institute, Cary, NC, USA). This study is registered with ClinicalTrials.gov (Number: NCT00284258).

Results

Patient populations

A total of 426 patients from 40 institutions in Japan were enrolled from January 2006 to January 2008, and randomised to receive either FOLFIRI or IRIS ($n = 213$ in each group; Fig. 1). The PPS population consisted of 203 patients in the FOLFIRI group and 198 in the IRIS group. All patients who received a study treatment [FOLFIRI ($n = 211$) and IRIS ($n = 210$)] were included in the safety evaluation. The baseline characteristics were well balanced between the two groups, as previously reported (Muro et al. 2010).

Treatment

The median number of courses of the protocol treatment was 4.0 (range 1–27) and 4.0 (range 1–23) in the FOLFIRI and IRIS groups, respectively. The median dose intensity relative to the planned dose intensity was irinotecan 78.3 %, bolus 5-FU 76.9 %, and infusional 5-FU 81.5 % in the FOLFIRI group, and irinotecan 78.3 % and S-1 88.9 % in the IRIS group. Treatments were discontinued because of PD in 71.8 % of the FOLFIRI group ($n = 153$) and 67.1 % of the IRIS group ($n = 143$). Treatment discontinuation owing to adverse events was more frequently observed in the IRIS group ($n = 49$, 23.0 %) than in the FOLFIRI group ($n = 28$, 13.1 %). Overall, 179 (84.8 %) patients in the FOLFIRI group and 184 (87.6 %) patients in the IRIS group required at least one dose delay or dose reduction at some point during the treatment course.

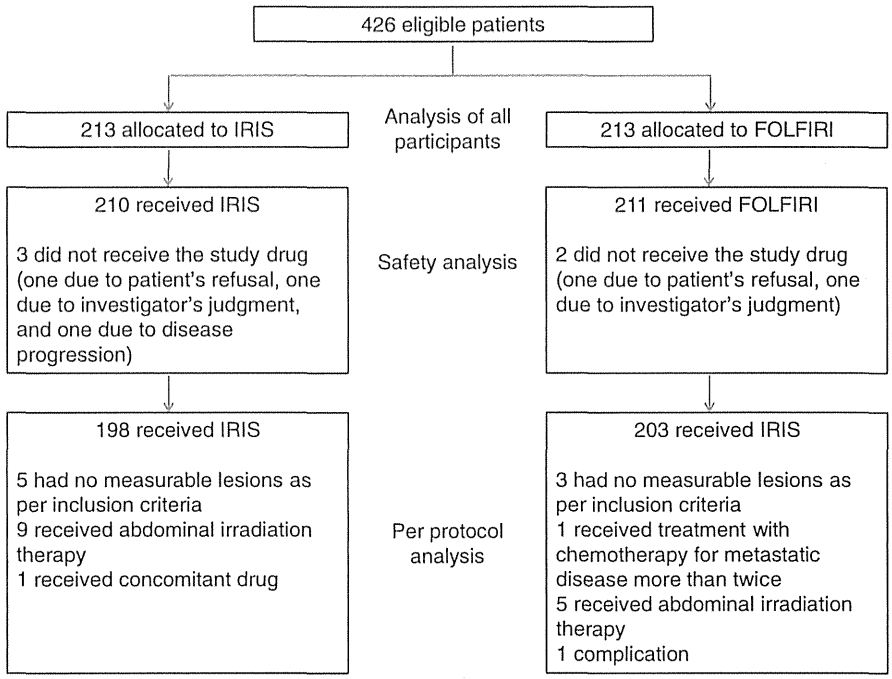

Fig. 1 Consort diagram. *IRIS* irinotecan plus S-1, *FOLFIRI* infusional 5-fluorouracil, folinic acid, and irinotecan

Third-line chemotherapy after failure of the protocol treatment in the second-line therapy was given to 168 (78.9 %) patients in the FOLFIRI group and 153 (71.8 %) patients in the IRIS group. In these patients, molecularly targeted agents were concomitantly used in 58 (27.2 %) patients (bevacizumab, 45; cetuximab, 17) in the FOLFIRI group and 52 (24.4 %) patients (bevacizumab, 38; cetuximab, 16) in the IRIS group, and no marked difference in the use of these agents was evident between the two groups (Table 1).

Table 1 Cancer treatment after discontinuation of the study treatment

Treatment	FOLFIRI *n* (%)	IRIS *n* (%)
No	45 (21.1)	60 (28.2)
Yes	168 (78.9)	153 (71.8)
Bevacizumab		
FOLFOX + bevacizumab	33 (15.5)	29 (13.6)
FOLFIRI + bevacizumab	19 (8.9)	12 (5.6)
5-FU/LV + bevacizumab	8 (3.8)	6 (2.8)
Cetuximab		
FOLFIRI + cetuximab	0 (0)	1 (0.5)
Irinotecan + cetuximab	16 (7.5)	13 (6.1)
FOLFOX	60 (28.2)	61 (28.6)
FOLFIRI	9 (4.2)	25 (11.7)
5-FU/LV	7 (3.3)	10 (4.7)
Irinotecan	8 (3.8)	20 (9.4)
S-1	35 (16.4)	7 (3.3)
Irinotecan + S-1	16 (7.5)	3 (1.4)
Operation	12 (5.6)	11 (5.2)
Radiation therapy	29 (13.6)	18 (8.5)
Other	48 (22.5)	45 (21.1)

FOLFIRI infusional 5-fluorouracil, folinic acid, and irinotecan, *IRIS* irinotecan plus S-1, *FOLFOX* 5-fluorouracil, LV, and oxaliplatin, *5-FU* 5-fluorouracil, *LV* leucovorin

Overall survival

As of 29 July 2010 when the data collection was finally cut off, 352 deaths (FOLFIRI, 178; IRIS, 174) were confirmed with a median follow-up of 39.2 months. A total of 125 censored cases resolved from the last cut-off that we reported. The median OS was 17.4 months in the FOLFIRI group and 17.8 months in the IRIS group (HR 0.900; 95 % CI 0.728–1.112; $p = 0.003$ for a non-inferiority margin of 1.333; Fig. 2a). In the PPS population, the median OS was 17.4 months in the FOLFIRI group and 17.4 months in the IRIS group (HR 0.905; 95 % CI 0.728–1.126). The Bayesian posterior probabilities that the HR of IRIS relative to FOLFIRI would be <1.333 and <1.15 were calculated to be >99.9 % and >98.7 %, respectively.

Progression-free survival

When the data collection was finally cut off, 412 events including an increase of 23 events from the primary analysis were confirmed. The median PFS was 5.1 months in the FOLFIRI group and 5.8 months in the IRIS group. In the ITT population, the HR for IRIS to FOLFIRI was

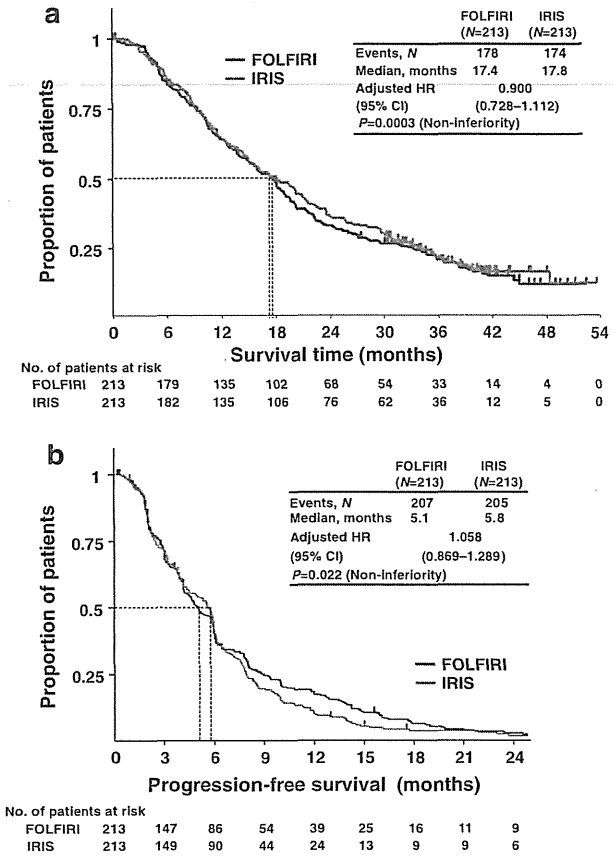

Fig. 2 OS (**a**) and PFS (**b**) in the intention-to-treat population. *IRIS* irinotecan plus S-1, *FOLFIRI* infusional 5-fluorouracil, folinic acid, and irinotecan, *HR* hazard ratio, *CI* confidence interval

1.058 (95 % CI 0.869–1.289; $p = 0.022$) and consistent with the primary analysis (Fig. 2b). In the PPS population, the median PFS was 5.1 months in the FOLFIRI group and 5.7 months in the IRIS group (HR 1.035; 95 % CI 0.843–1.271), being consistent with the primary analysis.

Subgroup analyses

Figure 3 shows the results of the subgroup analyses for OS. Except for the interaction of prior chemotherapy containing oxaliplatin (yes vs. no) and therapeutic effect, no interaction was observed between sex (male vs. female), age (<65 vs. 65–75 years), histological type (adenocarcinoma, well differentiated vs. moderately differentiated vs. poorly differentiated), or PS (0 vs. 1), and the therapeutic effect of IRIS was comparable to that of FOLFIRI.

In the subgroups of patients treated with FOLFIRI ($n = 128$) or IRIS ($n = 129$) who had received prior chemotherapy containing oxaliplatin, the median OS was 15.3 months in the IRIS group and 12.7 months in the FOLFIRI group (adjusted HR 0.755; 95 % CI 0.580–0.983), showing better survival in the IRIS group than in the FOLFIRI group (Fig. 4a). On the other hand, in the subgroups of patients treated with FOLFIRI ($n = 85$) or IRIS ($n = 84$) who had received prior chemotherapy without oxaliplatin, the median OS was more favourable in the FOLFIRI group than in the IRIS group (26.9 vs. 23.6 months; adjusted HR 1.229; 95 % CI 0.866–1.745) (Fig. 4b).

Safety

The results of the updated safety analysis were very similar to those previously reported (Muro et al. 2010). Briefly, specific adverse events were haematological toxicity (grade 3 or 4 neutropenia), which was observed in 52.1 % of the FOLFIRI group and 36.2 % of the IRIS group, and non-haematological toxicity (grade 3 diarrhoea), which was observed in 4.7 % of the FOLFIRI group and 20.5 % of the IRIS group. One treatment-related death from hypotension caused by shock was reported in the FOLFIRI group within 28 days after the end of the protocol treatment, while no treatment-related deaths were reported in the IRIS group.

Discussion

We conducted a phase 3 randomised study to compare FOLFIRI and IRIS as second-line chemotherapies for patients with mCRC. The primary analysis demonstrated the non-inferiority of IRIS to FOLFIRI for PFS as the primary endpoint. The secondary endpoints of OS and response rate were also equivalent between the two groups (Muro et al. 2010), but the data were immature with many cases censored at the primary analysis. In this updated analysis, data obtained 2.5 years after the end of the enrolment period (as pre-specified in the protocol) were included. The non-inferiority of IRIS to FOLFIRI for PFS as the primary endpoint was re-confirmed, and non-inferiority for OS was also demonstrated. In addition, the probabilities of HR < 1.333 and HR < 1.15, which are stricter non-inferiority margins for OS, were estimated to be >99.9 and >98.7 %, respectively, using Bayesian analyses. Our study results are highly robust.

When our study was started, FOLFOX was already one of the standard treatments worldwide, but oxaliplatin had just been launched and was rarely used in an adjuvant setting in Japan. Actually, 85 (39.9 %) patients in the FOLFIRI group and 84 (39.4 %) patients in the IRIS group had received prior chemotherapy without oxaliplatin. Most of these patients received prior chemotherapy in an adjuvant setting including tegafur-uracil with or without LV (27 patients in the FOLFIRI group and 32 in the IRIS group) or 5-FU/LV (11 patients in the FOLFIRI group and 7 in the IRIS group).

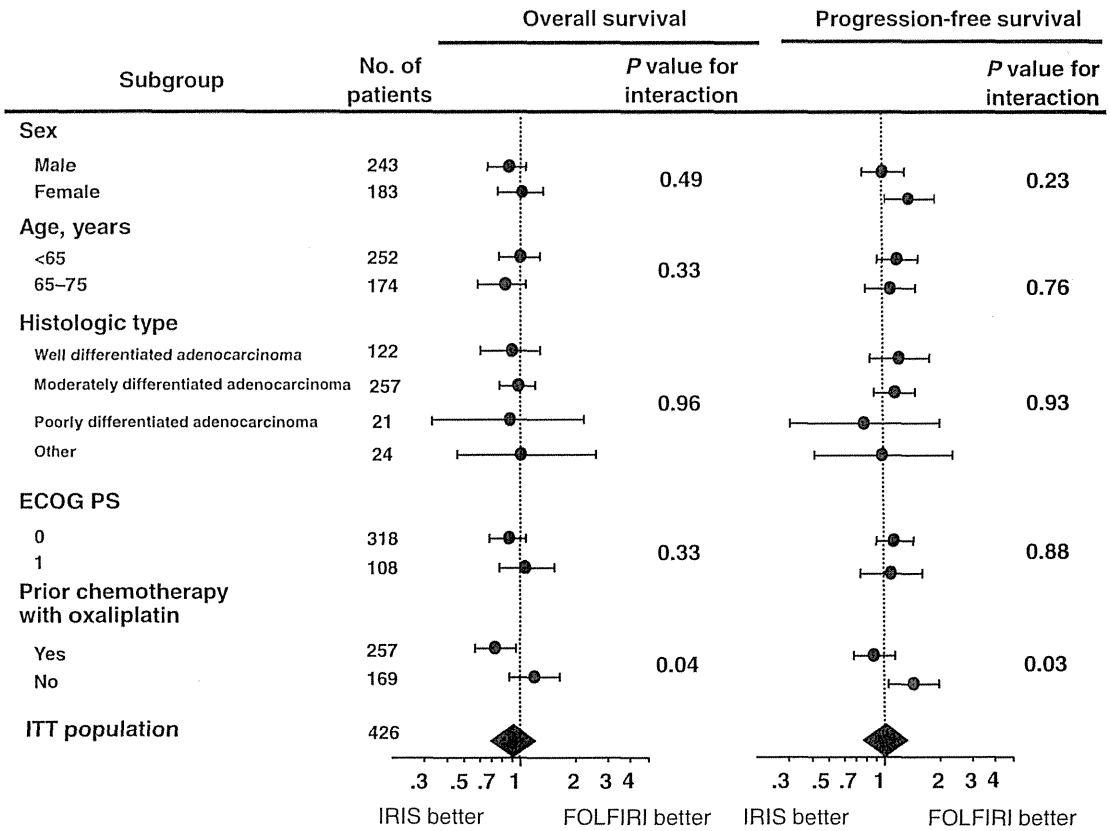

Fig. 3 Subgroup analyses of OS and PFS in the intention-to-treat (ITT) population. *IRIS* irinotecan plus S-1, *FOLFIRI* infusional 5-fluorouracil, folinic acid, and irinotecan

In the subgroup of patients who had received prior oxaliplatin, the adjusted HR for OS of IRIS to FOLFIRI was 0.755 (95 % CI 0.580–0.983), suggesting that IRIS might prolong the survival of patients who failed in first-line chemotherapy with oxaliplatin-containing regimens, compared with FOLFIRI. On the other hand, in the subgroup of patients who had received prior chemotherapy without oxaliplatin, the median OS was longer in the FOLFIRI group than in the IRIS group (adjusted HR 1.229; 95 % CI 0.866–1.745). Interactions between prior chemotherapy and therapeutic effects in the two groups may need to be considered.

There are some possible reasons for the interactions. Resistance to 5-FU/LV shared by patients receiving first-line FOLFOX and second-line FOLFIRI may be overcome to some extent by the dihydropyrimidine dehydrogenase (DPD) inhibitor contained in S-1. On the other hand, it is also speculated that cross-resistance to DPD inhibitory agents may be partly overcome by bolus 5-FU/LV in patients receiving FOLFIRI (Baba et al. 2012), considering the fact that many patients in the subset without prior oxaliplatin received adjuvant chemotherapy with DPD inhibitory agents as a prior therapy. However, further studies, including basic studies, are needed to clarify this finding.

In recent phase 3 trials of molecularly targeted agents used in second-line chemotherapy regimens, the median OS was reported to be 10.7–14.5 months in groups treated with anti-EGFR antibodies. The survival data in the present study seemed to be consistent with the survival data in these recent studies of molecularly targeted agents (Sobrero et al. 2008; Peeters et al. 2010).

In conclusion, this study has demonstrated that IRIS is non-inferior to FOLFIRI not only for PFS, but also for OS as second-line chemotherapy for mCRC. Thus, IRIS should be considered as a treatment option. In particular, IRIS may be a favourable regimen for patients previously treated with chemotherapy containing oxaliplatin. To further improve the outcome, future studies of both first-line and second-line therapies are warranted to evaluate IRIS in combination with molecularly targeted agents such as bevacizumab, cetuximab, and panitumumab.

Acknowledgments We thank all of the patients, their families, and the institutions involved in this study (see "Appendix"). The authors also thank Yuh Sakata, Yasuo Ohashi, and Nobuyuki Yamamoto for the Independent Data Monitoring Committee, and Atsushi Ohtsu, Yasuaki Arai, and Junji Tanaka for the Independent Central Review Committee for their contributions to this report. The authors dedicate this

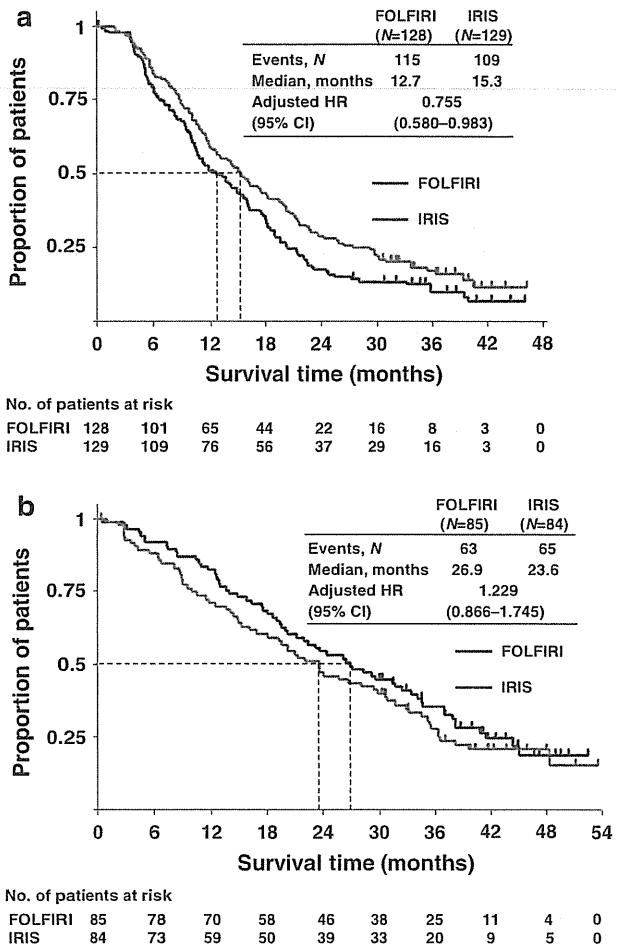

Fig. 4 Survival according to prior chemotherapy with oxaliplatin (**a**) or without oxaliplatin (**b**). *IRIS* irinotecan plus S-1, *FOLFIRI* infusional 5-fluorouracil, folinic acid, and irinotecan, *HR* hazard ratio, *CI* confidence interval

article to the memory of Prof. Hiroya Takiuchi, who contributed to the conception and design of this study. The senior academic authors designed the trial in cooperation with the study sponsors. The sponsors provided funding and organisational support, collected data, and performed analyses, but did not undertake any data interpretation. This report was written by the corresponding author (with additional input from the other authors), who had unrestricted access to the raw study data, gives assurance for the accuracy and completeness of the reported analyses, and had final responsibility for the decision to submit for publication. This work was funded by Taiho Pharmaceutical Co. Ltd., Japan, and Daiichi Sankyo Co. Ltd., Japan.

Conflict of interest The authors declare no conflict of interest.

Appendix (participating institutes): FIRIS Study Group

List of participating institutions in order of patient recruitment:

Shizuoka Cancer Center (Shizuoka, Japan); Aichi Cancer Center Hospital (Nagoya, Japan); National Cancer Center Hospital (Tokyo, Japan); Kochi Health Sciences Center (Kochi, Japan); Gunma Prefectural Cancer Center (Gunma, Japan); Kumamoto University Hospital (Kumamoto, Japan); Kinki University School of Medicine (Osaka, Japan); Chiba Cancer Center (Chiba, Japan); Nagoya Memorial Hospital (Nagoya, Japan); National Hospital Organization Shikoku Cancer Center (Matsuyama, Japan); Saitama Cancer Center (Saitama, Japan); Osaka Medical College Hospital (Takatsuki, Japan); National Kyushu Cancer Center (Fukuoka, Japan); Osaka City General Hospital (Osaka, Japan); Gunma University Graduate School of Medicine (Maebashi, Japan); Hokkaido University Hospital Cancer Center (Sapporo, Japan); National Hospital Organization Kyoto Medical Center (Kyoto, Japan); Keio University Hospital (Tokyo, Japan); Kansai Rosai Hospital (Hyogo, Japan); Tokyo Medical and Dental University (Tokyo, Japan); Osaka Medical Center for Cancer and Cardiovascular Diseases (Osaka, Japan); Aomori Prefectural Central Hospital (Aomori, Japan); Showa University Toyosu Hospital (Tokyo, Japan); Minoh City Hospital (Osaka, Japan); Saiseikai Kumamoto Hospital (Kumamoto, Japan); Toyama University Hospital (Toyama, Japan); National Hospital Organization Kagoshima Medical Center (Kagoshima, Japan); Tonan Hospital (Sapporo, Japan); Kanagawa Cancer Center (Yokohama, Japan); Niigata Cancer Center Hospital (Niigata, Japan); Saku Central Hospital (Nagano, Japan); Hyogo Cancer Center (Hyogo, Japan); Hiroshima University Hospital (Hiroshima, Japan); Tomakomai Nissho Hospital (Hokkaido, Japan); Aichi Cancer Center Aichi Hospital (Aichi, Japan); National Hospital Organization Nagoya Medical Center (Nagoya, Japan); Kobe University Hospital (Kobe, Japan); Yamagata Prefectural Central Hospital (Yamagata, Japan); Yokohama City University Hospital (Yokohama, Japan); and Kitasato University East Hospital (Kanagawa, Japan).

References

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 107:1950–1955

Brookmeyer R, Crowley J (1982) A confidence interval for the median survival time. Biometrics 38:29–41

Fuse N, Doi T, Ohtsu A et al (2008) Safety of irinotecan and infusional fluorouracil/leucovorin (FOLFIRI) in Japan: a retrospective review of 48 patients with metastatic colorectal cancer. Int J Clin Oncol 13:144–149

Goto A, Yamada Y, Yasui H et al (2006) Phase II study of combination therapy with S-1 and irinotecan in patients with advanced colorectal cancer. Ann Oncol 17:968–973

Komatsu Y, Yuki S, Fuse N et al (2010) Phase 1/2 clinical study of irinotecan and oral S-1 (IRIS) in patients with advanced gastric cancer. Adv Ther 27:483–492

Komatsu Y, Yuki S, Sogabe S et al (2011) Phase II study of combined treatment with irinotecan and S-1 (IRIS) in patients with inoperable or recurrent advanced colorectal cancer (HGCSG0302). Oncology 80:70–75

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 11:853–860

National Comprehensive Cancer Network (2014a) NCCN Clinical Practice Guidelines in Oncology: Colon Cancer, version 3.2014. http://www.nccn.org/professionals/physician_gls/f_guidelines.asp. Accessed May 20 2014

National Comprehensive Cancer Network (2014b) NCCN Clinical Practice Guidelines in Oncology: Rectal Cancer, version 3.2014. http://www.nccn.org/professionals/physician_gls/f_guidelines.asp. Accessed May 20 2014

O'Neil BH, Goldberg RM (2008) Innovations in chemotherapy for metastatic colorectal cancer: an update of recent clinical trials. The Oncol 13:1074–1083

Peeters M, Price TJ, Cervantes A et al (2010) Randomized phase III study of panitumumab with fluorouracil, leucovorin, and irinotecan (FOLFIRI) compared with FOLFIRI alone as second-line treatment in patients with metastatic colorectal cancer. J Clin Oncol 28:4706–4713

Schmoll HJ, Van Cutsem E, Stein A et al (2012) ESMO Consensus Guidelines for management of patients with colon and rectal cancer. a personalized approach to clinical decision making. Ann Oncol 23:2479–2516

Shiozawa M, Akaike M, Sugano N et al (2010) A phase II study of combination therapy with irinotecan and S-1 (IRIS) in patients with advanced colorectal cancer. Cancer Chemother Pharmacol 66:987–992

Sobrero AF, Maurel J, Fehrenbacher L et al (2008) EPIC: phase III trial of cetuximab plus irinotecan after fluoropyrimidine and oxaliplatin failure in patients with metastatic colorectal cancer. J Clin Oncol 26:2311–2319

Spiegelhalter DJ, Freedman LS, Parmar MKB (1994) Bayesian approaches to randomized trials. J R Stat Soc 157:357–387

Tournigand C, André 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 22:229–237

Tsunoda A, Yasuda N, Nakao K et al (2009) Phase II study of S-1 combined with irinotecan (CPT-11) in patients with advanced colorectal cancer. Oncology 77:192–196

ANTICANCER RESEARCH *35*: 371-378 (2015)

Reduced Dose of Salvage-line Regorafenib Monotherapy for Metastatic Colorectal Cancer in Japan

GEN HIRANO[1], AKITAKA MAKIYAMA[1], CHINATSU MAKIYAMA[1], TAITO ESAKI[2], HISANOBU ODA[2], KEITA UCHINO[3], MASATO KOMODA[3], RISA TANAKA[4], YUZO MATSUSHITA[4], KENJI MITSUGI[4], YOSHIHIRO SHIBATA[5], HOZUMI KUMAGAI[6], SHUJI ARITA[6,7], HIROSHI ARIYAMA[6], HITOSHI KUSABA[6], KOICHI AKASHI[6] and EISHI BABA[7]

[1]*Department of Hematology and Oncology, Japan Community Health Care Organization Kyushu Hospital, Kitakyushu, Japan;*
[2]*Department of Gastrointestinal and Medical Oncology, National Kyushu Cancer Center, Fukuoka, Japan;*
[3]*Department of Medical Oncology, Clinical Research Institute, National Hospital Organization Kyushu Medical Center, Fukuoka, Japan;*
[4]*Department of Oncology, Hamanomachi Hospital, Fukuoka, Japan;*
[5]*Department of Chemotherapy, Miyazaki Prefectural Miyazaki Hospital, Miyazaki, Japan;*
[6]*Department of Hematology and Oncology of Kyushu University Hospital, Fukuoka, Japan;*
[7]*Department of Comprehensive Clinical Oncology, Faculty of Medical Sciences, Kyushu University, Fukuoka, Japan*

Abstract. *Background: Salvage-line regorafenib monotherapy exhibited a marked survival benefit for metastatic colorectal cancer (mCRC). However, the toxicity of this regimen has resulted in the clinical use of a reduced dose of regorafenib. Patients and Methods: Thirty-two Japanese mCRC patients (median age=61 years) who had been treated with regorafenib were retrospectively examined. Results: Best objective response rate was 0% and stable disease (SD) was 31%. Median progression-free survival was 81 days and median overall survival was 233 days. Adverse events of any grade were observed in all patients: 17 (53%) patients suffered grade 3 or 4 adverse events including fatigue (13%), anorexia (13%), hand-foot skin reaction (22%) and elevations of alanine aminotransferase/aspartate aminotransferase (19%/16%). One patient with grade 5 liver dysfunction was identified (3%). Twenty-nine (91%) patients required treatment dose reduction or a delay in treatment. The relative dose intensity was 59%. Regorafenib treatments were terminated because of disease progression (59%) or adverse events (34%). Conclusion: Despite a decrease in the intensity of regorafenib treatment, because of severe adverse events, a fairly favorable efficacy was achieved in Japanese patients.*

Correspondence to: Eishi Baba, MD, Ph.D., Department of Comprehensive Clinical Oncology, Faculty of Medical Sciences, Kyushu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka 812-8582, Japan. Tel: +81 926426921, Fax: +81 926426922, e-mail: e-baba@c-oncology.med.kyushu-u.ac.jp

Key Words: Regorafenib, metastatic colorectal cancer, chemotherapy, adverse events.

Colorectal cancer (CRC) is the third most common cancer and the fourth most common cause of death in the world (1). In Japan, CRC is the third most common cause of death and the number of annual deaths continues to increase (2). While surgical treatments are performed for patients with localized disease, at least 50% of CRC patients will develop distant metastases and are, therefore, inoperable (3). Systemic chemotherapy has been developed as a standard therapy against metastatic CRC (mCRC), and therapeutic outcomes have since improved. Combination chemotherapy regimens with cytotoxic drugs, such as oxaliplatin, irinotecan and fluoropyrimidine, and with molecular-targeting drugs, such as anti-vascular endothelial growth factor (VEGF) and anti-epidermal growth factor receptor (EGFR) antibodies, can extend survival time in mCRC patients. Recent clinical studies showed that a median overall survival of 30 months was achieved in mCRC patients (4). However, tumors often become resistant to these agents and show disease progression despite chemotherapies. Therefore, further therapeutic options are required.

Regorafenib is an oral multi-kinase inhibitor that interferes with multiple signaling pathways that participate in the proliferation and survival of CRC cells, including those mediating angiogenesis, oncogenesis and maintenance of tumor microenvironment (5). The global phase 3 CORRECT study (Regorafenib Monotherapy for Previously Treated

0250-7005/2015 $2.00+.40

Metastatic Colorectal Cancer) assessed the efficacy and safety of regorafenib monotherapy *vs.* placebo for mCRC patients after failure of standard chemotherapy that included oxaliplatin, irinotecan, fluoropyrimidine, bevacizumab and anti-EGFR antibodies in case of *KRAS* wild-type status (6). A total of 760 patients (83% from Western countries in 83%, 14% from Asian countries, 3% from Eastern Europe countries) were randomly assigned to a regorafenib arm or a placebo arm at the rate of 2 to 1. The CORRECT study demonstrated that overall survival (OS) was significantly better in the regorafenib group than in the placebo group and, thus, regorafenib monotherapy was subsequently approved as an agent for salvage-line chemotherapy of mCRC in 2012 in the United States and the European Union and in 2013 in Japan. Additionally, regorafenib was proven to be effective for patients with metastatic gastrointestinal stromal tumors, as demonstrated in a phase III clinical study (GRID study) (7).

In the CORRECT study, Common Terminology Criteria for Adverse Events (CTC-AE) grade 3 and higher toxicity occurred in 14% of the placebo group and in 54% in the regorafenib group. Hand-foot skin reaction, fatigue, diarrhea, hypertension and rash or desquamation was frequently observed and, thus, intensive maintenance for these adverse events was required. In terms of adverse events related to anti-angiogenic activity, grade 5 cerebrovascular events and bleeding from the lung, rectum and vagina were reported. One death also occurred due to liver dysfunction. While the toxicity of this regimen has resulted in the clinical use of a reduced dose of regorafenib, the actual efficacy and safety profiles of this reduced-dose regimen has not yet been studied. Therefore, the goal of the present study was to investigate the efficacy and safety of reduced-dose regorafenib for treatment of mCRC in Japan.

Patients and Methods

Patients. The present study retrospectively investigated 32 patients with pathohistologically-proven unresectable, recurrent or metastatic colorectal adenocarcinoma. All patients received regorafenib monotherapy from February 1, 2011 to January 8, 2014 at one of the following six Institutions: Department of Hematology and Oncology, Japan Community Health Care Organization Kyushu Hospital; Department of Gastrointestinal and Medical Oncology of National Kyushu Cancer Center; Department of Medical Oncology in Hamanomachi Hospital; Department of Medical Oncology, National Hospital Organization Kyushu Medical Center; Department of Chemotherapy, Miyazaki Prefectural Miyazaki Hospital; Department of Hematology and Oncology of Kyushu University Hospital, Fukuoka, Japan. Information regarding all cases was obtained from medical records from each institution. Patient background characteristics were recorded and included age, sex, Eastern Cooperative Oncology Group (ECOG) performance status (PS), primary site of the tumor, *KRAS* mutational status and history of prior chemotherapies. In patients who were treated with regorafenib during this survey period, administration doses and schedule, best therapeutic effects and adverse events were investigated. Progression-free survival (PFS) was defined as the period from the initiation of the therapy to the day of tumor progression or the day of any caused death. OS was defined as the period from initiation of the therapy to the day of any caused death. Each reason for therapeutic dose reduction before and during regorafenib administration was also examined. The present study was carried out according to the regulations of local ethics committee of each institution and according to the Declaration of Helsinki.

Treatment. All patients had been treated with one or more regimens of systemic chemotherapy and found non-responsive or did not tolerate the regimen. The study treatment of regorafenib was administered until disease progression, unacceptable toxicity or the decision to discontinue by the patient or the investigator. The treatment dose of regorafenib was 160 mg/day *per os* (*p.o.*) for the first 21 days of each 28-day cycle. In cases of adverse events, the dose was reduced to 120 mg/day or 80 mg/day; otherwise, administration of regorafenib was suspended until recovery from the adverse events. Therapeutic dose reduction and treatment delay were performed according to the dose modification/interruption protocol of the CORRECT study (6). Additional modification of therapy was carried-out based on the investigators' decisions considering symptoms and laboratory data of patients.

Assessments. In the first treatment cycle, patients were hospitalized or visited the outpatient office weekly. Patients were assessed for adverse events by physical examination, urinalysis, blood cell counts and serum chemistry at every visit. All adverse events were evaluated according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTC-AE) version 4.0. The most severe grades of adverse events during chemotherapy were recorded. Assessment of tumor regions was performed by computed tomography (CT) scan, gastrointestinal endoscopy and magnetic resonance imaging (MRI) every 4-12 weeks.

Statistics. Sub-groups based on the patients characteristics or the relative dose-intensity of regorafenib in terms of OS were separately analyzed by the log-rank test.

Results

Patients' background and treatments. Thirty-two patients were treated with regorafenib monotherapy during the observation period. Their median age was 61 years (range=30-78 years) and the population included 18 (56%) males (Table I). ECOG PS was 0 in eight cases (25%), 1 in 21 cases (66%) and 2 in three cases (9%). The primary affected organ was the colon in 19 cases (59%) and the rectum in 13 cases (41%). The primary site was resected in 21 cases. All cases were histologically diagnosed as adenocarcinoma. Wild-type *KRAS* exon 2 was identified in 22 cases (69%) and mutated *KRAS* type was identified in nine cases (28%). One case had uncertain *KRAS* exon 2 status, whereas other kinds of gene alterations of the tumors were not examined. Two regimens of prior chemotherapy were performed in 15 cases (47%), three regimens of prior chemotherapy were performed in 10 cases (31%) and more

Table I. *Baseline patients' characteristics.*

Characteristic	No.	%
Gender		
Male	18	56
Female	14	44
Age		
Median (range), years	61	(30-78)
Performance status		
0	8	25
1	21	66
2	3	9
Primary tumor		
Colon	19	59
Rectum	13	41
Resected	21	66
Remaining	11	34
Histology		
Adenocarcinoma	32	100
Others	0	0
KRAS mutational status		
Wild-type	22	69
Mutant-type	9	28
Not tested	1	3
Prior chemotherapy (regimens)		
2	15	47
3	10	31
4 or more	7	22
Prior bevacizumab therapy	25	78
Prior EGFR antibody	23	72

EGFR, Epithelial growth factor receptor.

Table II. *Efficacy of regorafenib monotherapy.*

Best objective response	No.	%
CR	0	0
PR	0	0
SD	10	31
non-CR/non-PD	1	3
PD	17	53
NE	4	13
Response rate	0	0
Disease control rate	11	34

CR, Complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluable.

than four regimens of prior chemotherapy were performed in seven cases (22%). Twenty-five cases (78%) had prior bevacizumab therapy and the other seven cases had no history of bevacizumab treatment even though they did not have any complications, which were contraindicated to anti-angiogenesis inhibitors. Anti-EGFR antibodies were administered in 22 cases (69%) with wild-type *KRAS* exon 2 and in one case (3%) with unknown *KRAS* status.

Table III. *Characteristics of regorafenib monotherapy.*

Characteristics	No.	%
Duration of therapy		
Median weeks (range)	10.9	(0.6-51.9)
Relative dose intensity (%)	59	(24-100)
Dose reduction or interrupt dose		
Total	29	91
Dose reduction prior to the therapy	7	22
Dose reduction during therapy	22	69
Reasons for the dose reduction prior to the therapy		
Complication other than liver disease	1	
Complication of liver disease	1	
Poor performance status	1	
Predicted adverse events	2	
Reasons for the dose reduction during therapy		
Adverse events	22	
Reasons for the termination of therapy		
Progressive disease	19	59
Adverse events	11	34
Others	2	6

Treatment. The median regorafenib treatment period was 10.9 weeks (range=0.6-51.9 weeks) and the median relative dose intensity was 59% (range=24-100%) (Table III). In this study, patients were followed until July 8, 2014. At that point, administration of regorafenib was terminated in all cases. Twenty-two patients had died, six patients remained alive and four patients were lost to follow-up. In the present study, dose modification and treatment delay of regorafenib were performed in 29 cases (91%). Reduced-dose administration of regorafenib in the initial cycle of the therapy was observed in seven cases (22%) (120 mg/day in five cases, and 80 mg/day in two cases). The reasons for the initial dose reduction included liver dysfunction in three cases, complications other than liver dysfunction in one, poor PS in one case and suspected severe adverse events in two cases. On the other hand, dose reduction and treatment delay in 22 cases were caused by adverse events. Regorafenib treatment was terminated because of tumor progression in 19 cases (59%), adverse events in 11 cases (34%) and other reasons in two cases (6%).

Efficacy. None of the cases achieved complete response (CR) or partial response (PR). Ten cases (31%) showed stable disease (SD), one case (3%) showed non-CR/non-progressive disease (PD), 17 cases (53%) showed PD and four cases (13%) were not evaluable (NE) (Table II). The objective response rate was 0% and the disease control rate

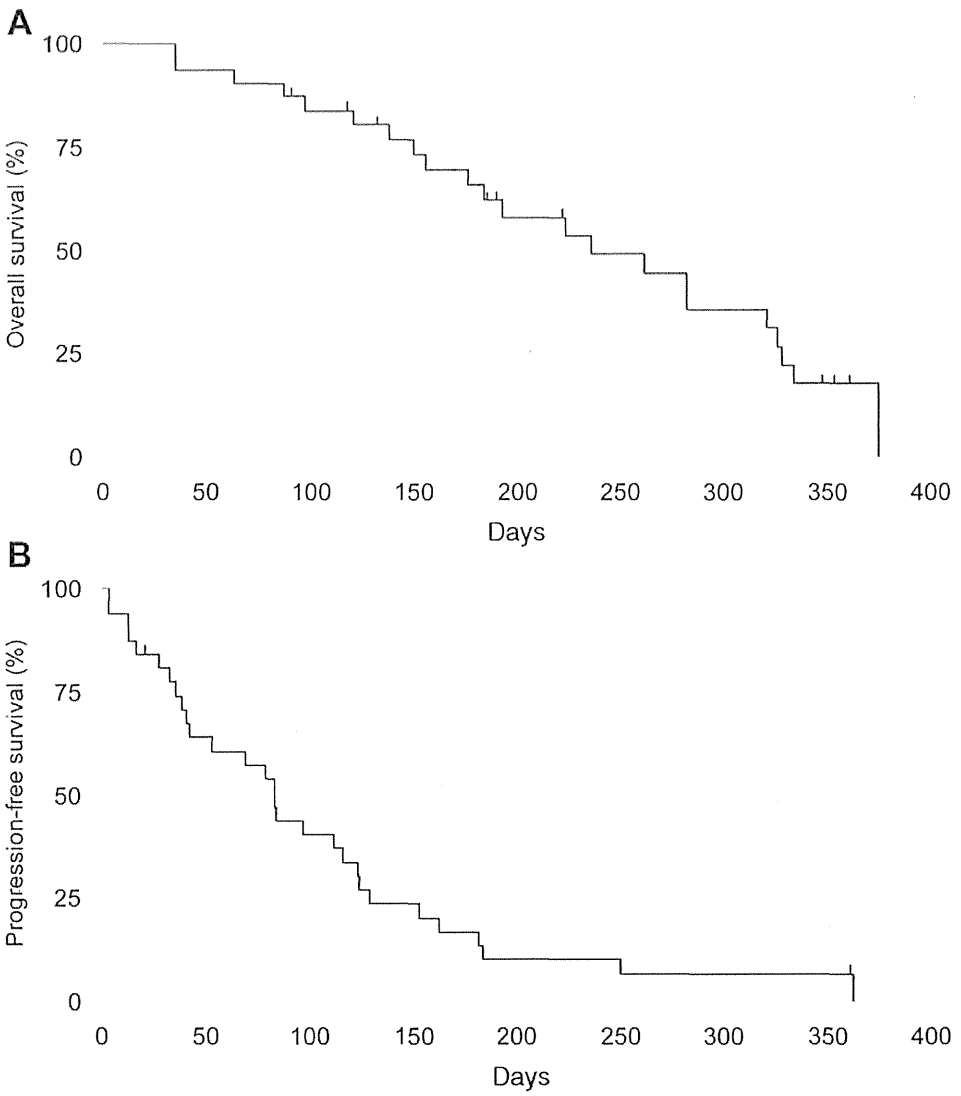

Figure 1. *Overall survival and progression free survivals. Kaplan-Meier estimates for overall survival (A) and progression free survival (B) in the whole examined population (n=32).*

(CR+PR+SD+non-CR/non-PD) was 34%. Median PFS was 81 days (4-363) and median OS was 233 days (32-375) (Figure 1A, B).

Safety. Therapy-related toxicities in the patients were assessed according to CTC-AE version 4.0 and the worst grade is shown in Table IV. Concerning hematological toxicities, thrombocytopenia was observed in 44% (grade 3/4; 6%), anemia in 56% (grade 3/4; 3%) and leukocytopenia in 19% (grade 3/4; 0%). No febrile neutropenia was recorded.

In terms of non-hematological toxicities, fatigue was observed in 47% of patients (grade 3/4; 13%), hand-foot skin reaction in 72% (grade 3/4; 22%), anorexia in 41% (grade 3/4; 13%), stomatitis in 25% (grade 3/4; 3%) and diarrhea in 6% (grade 3/4; 3%). Serum chemistry examination revealed that increments of aspartate aminotransferase (AST), alanine aminotransferase (ALT) and total bilirubin were found in 81%, 59% and 50% of all the patients, respectively (grade 3/4; 19%, 16%, 9%). Unfortunately, grade 5 liver dysfunction occurred in one female patient in her 30s who had sigmoid colon cancer with multiple liver metastases. Her prior chemotherapies consisted of the combination of oxaliplatin and 5-FU (FOLFOX) plus bevacizumab and the combination of irinotecan and 5-FU (FOLFIRI) plus panitumumab. A

Table IV. *Adverse events.*

Adverse event	All grades		Grade 3		Grade 4		Grade 5	
	N	%	N	%	N	%	N	%
Fatigue	15	47	4	13	0	0	0	0
Hand-foot skin reaction	23	72	7	22	0	0	0	0
Hypertension	15	47	3	9	0	0	0	0
Anorexia	13	41	4	13	0	0	0	0
Skin eruption	9	28	2	6	0	0	0	0
Nausea/Vomiting	1	3	1	3	0	0	0	0
Stomatitis	8	25	1	3	0	0	0	0
Diarrhea	2	6	1	3	0	0	0	0
Proteinuria	1	3	1	3	0	0	0	0
Pneumonia	1	3	1	3	0	0	0	0
Stevens-Johnson syndrome	1	3	1	3	0	0	0	0
Hepatic failure	1	3	0	0	0	0	1	3
Leukocytopenia	6	19	0	0	0	0	0	0
Anemia	18	56	1	3	0	0	0	0
Thrombocytopenia	14	44	2	6	0	0	0	0
Albumin decreased	22	69	0	0	0	0	0	0
AST increase	26	81	3	9	3	9	0	0
ALT increase	19	59	2	6	3	9	0	0
LDH increase	22	69	2	6	0	0	0	0
Total bilirubin increase	16	50	1	3	2	6	0	0

AST, Aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase.

slight increase in serum AST and total bilirubin occurred at 22 days after the initiation of standard-dose regorafenib and liver dysfunction progressed even after termination of regorafenib administration on day 22. The patient died on day 35 despite various liver supporting therapies.

Subgroup analysis. Patients were stratified with respect to a broad range of background characteristics and OS was compared between these groups using the log-rank test (Table V). No differences in OS were seen when stratifying patients according to age, sex, primary disease site or prior chemotherapies (including a history of bevacizumab therapy and number of regimens). Patients with PS of 2 showed significantly worse outcomes when compared to those with PS 0 or 1, suggesting that PS 0 or 1 before regorafenib therapy could be a valuable indication to start therapy. Also, patients with *KRAS* wild-type status showed a tendency towards favorable OS when compared with patients with *KRAS* exon 2 mutation (Table V).

Table V. *Sub-group analysis of overall survival.*

Factors	Valuables	No.	p-Value
Age	<65 years	22	0.95
	>66 years	10	
Gender	Male	18	0.94
	Female	14	
PS	0/1	29	<0.001
	2	3	
Primary site	Colon	19	0.21
	Rectum	13	
KRAS	Wild-type	22	0.025
	Mutant-type	9	
Prior regimens	1/2	16	0.17
	3 or more	16	
Prior bevacizumab	Yes	25	0.17
	No	7	
Relative dose intensity	>59%	16	0.22
	<59%	16	

PS, Performance status.

Discussion

The relative dose intensity of regorafenib monotherapy in the present study was 59% when compared to a 78.9% relative dose intensity reported in a previous phase III trial (CORRECT study). The CORRECT study demonstrated a significant survival benefit of salvage-line regorafenib monotherapy over best supportive care for patients with advanced colorectal cancer (6). The decreased relative dose intensity is reflected by dose reduction and treatment delay