Overview

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Title: A Phase I/II Study of XELIRI Plus Bevacizumab as Second-Line Chemotherapy for Japanese Patients With Metastatic Colorectal Cancer (BIX Study)

Authors: Yasuo Hamamoto,[a] Tatsuro Yamaguchi,[b] Tomohiro Nishina,[c] Kentaro Yamazaki,[d] Takashi Ura,[e] Takako Nakajima,[f] Ayumu Goto,[g] Ken Shimada,[h] Norisuke Nakayama,[i] Junichi Sakamoto,[j] Satoshi Morita,[k] Yasuhide Yamada[l]

[a]Keio Cancer Center, School of Medicine, Keio University, Tokyo, Japan; [b]Department of Surgery, Tokyo Metropolitan Cancer and Infectious Disease Center, Komagome Hospital, Tokyo, Japan; [c]Department of Gastrointestinal Medical Oncology, National Hospital Organization Shikoku Cancer Center, Ehime, Japan; [d]Division of Gastrointestinal Oncology, Shizuoka Cancer Center, Shizuoka, Japan; [e]Department of Clinical Oncology, Aichi Cancer Center Central Hospital, Nagoya, Japan; [f]Department of Medical Oncology, St. Marianna University School of Medicine, Kanagawa, Japan; [g]Department of Clinical Oncology, Yokohama City University Hospital, Kanagawa, Japan; [h]Department of Medical Oncology, Showa University Northern Yokohama Hospital, Kanagawa, Japan; [i]Department of Gastroenterology, Kanagawa Cancer Center Hospital, Kanagawa, Japan; [j]Director, Tokai Central Hospital, Gifu, Japan; [k]Department of Biostatistics and Epidemiology, Graduate School of Medicine, Kyoto University, Kyoto, Japan; [l]Gastrointestinal Oncology Division, National Cancer Center Hospital, Tokyo, Japan

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Principal Investigator: Yasuhide Yamada

IRB Approved: Yes

Disclosures

Tatsuro Yamaguchi: Taiho Pharmaceutical Co., Ltd., Chugai Pharmaceutical Co., Ltd. (H); **Tomohiro Nishina:** Chugai Pharmaceutical Co., Ltd., Yakult Honsha Co., Ltd. (H); **Kentaro Yamazaki:** Chugai Pharmaceutical Co., Ltd., Yakult Honsha Co., Ltd. (H); **Takako Nakajima:** Chugai Pharmaceutical Co., Ltd., (RF, H); **Ayumu Goto:** Chugai Pharmaceutical Co., Ltd. (H); **Yasuhide Yamada:** Chugai Pharmaceutical Co., Ltd., Yakult Honsha Co., Ltd. (H); Chugai Pharmaceutical Co., Ltd. (RF); **Satoshi Morita:** Chugai Pharmaceutical Co., Ltd. (H). The other authors indicated no financial relationships.

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

Author Summary: Abstract and Brief Discussion

Background

Capecitabine is used mainly with oxaliplatin to treat metastatic colorectal cancer (mCRC) [1, 2]. Results from capecitabine plus irinotecan (XELIRI) with or without bevacizumab (BV) have been reported in Europe but not in Japan [3–10]. Consequently, the safety and efficacy of XELIRI plus BV in Japanese patients with mCRC were assessed in a single-arm phase II study.

Methods

Eligible patients had had prior chemotherapy containing BV for mCRC and wild-type or heterozygous UGT1A1. Therapy in each 21-day treatment cycle consisted of capecitabine (800 mg/m^2 twice daily on days 1–15), irinotecan (200 mg/m^2 on day 1), and BV (7.5 mg/kg on day 1). The primary endpoint was dose-limiting toxicity in phase I and progression-free survival (PFS) in phase II.

Results

A total of 34 patients (6 in phase I, 28 in phase II) were enrolled from May 2010 to June 2011. Baseline characteristics included a median age of 60 years (range: 22–74 years) for 24 men and 10 women (Table 2). No dose-limiting toxicities appeared in phase I. Median PFS was 240 days (95% confidence interval: 179–311 days). Overall response rate was 18.1%, and the disease-control rate was 90.9%. The incidence of adverse events frequently associated with irinotecan and capecitabine were neutropenia (any grade, 55.9%; grade 3 or 4, 11.8%), diarrhea (any grade, 50%; grade 3 or 4, 5.9%), and hand-foot syndrome (any grade, 61.8%; grade 3 or 4, 5.9%) (Table 4).

Conclusion

Our results suggest that XELIRI plus BV is well tolerated and effective as a second-line treatment for mCRC in Japanese patients. This regimen could be especially appropriate for patients resistant to oxaliplatin-based regimens.

Discussion

In this prospective trial for Japanese patients with metastatic colorectal cancer, capecitabine plus irinotecan (XELIRI) plus bevacizumab as a second-line regimen achieved longer progression-free survival (240 days) and a higher overall response rate (18.1%) than other reported regimens, with an acceptable tolerability profile (Table 3). Unlike FOLFIRI, XELIRI doses do not require a long infusion process or an infuser pump, providing a great advantage to patients. The key finding in this study was that XELIRI plus bevacizumab demonstrated promising results beyond progression in Japanese patients.

Trial Information

Disease	Colorectal cancer
Stage of disease / treatment	Metastatic / Advanced
Prior Therapy	1 prior regimen
Type of study - 1	Phase II
Type of study - 2	Single arm
Primary Endpoint	Progression-free survival
Secondary Endpoint	Overall response rate
Secondary Endpoint	Overall survival
Additional Details of Endpoints or Study Design	Phase I part: the primary endpoint was estimated dose-limiting toxicity in the first cycle. Another secondary endpoint was adverse events.
Investigator's Analysis	Active and should be pursued further

Drug Information

Drug 1 **Generic/Working name**	Capecitabine
Trade name	XELODA
Company name	Chugai Pharmaceutical Co., Ltd. (Tokyo, Japan).
Drug type	Other
Drug class	Antimetabolite
Dose	1,600 mg/m^2
Route	Oral (p.o.)
Schedule of Administration	2 divided administrations daily on days 1–14 of each 21-day cycle
Drug 2 **Generic/Working name**	Irinotecan
Trade name	Campto/Topotecin
Company name	Yakult Honsha/Daiichi Sankyo Company
Drug type	Other
Drug class	Topoisomerase I
Dose	200 mg/m^2

Route	IV
Schedule of Administration	On day 1 in each 21-day cycle
Drug 3 **Generic/Working name**	Bevacizumab
Trade name	Avastin
Company name	Chugai Pharmaceutical Co., Ltd. (Tokyo, Japan).
Drug type	Antibody
Drug class	Angiogenesis - VEGF
Dose	7.5 mg/kg
Route	IV
Schedule of Administration	On day 1 in each 21-day cycle

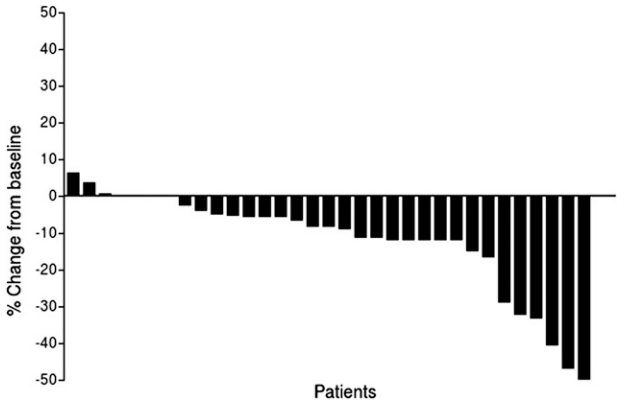
Patient Characteristics

Number of patients, male	24
Number of patients, female	10
Stage	Stage IV/Recurrent
Age	Median (range): 60 (22–74)
Number of prior systemic therapies	Median (range): 1
Performance Status:	ECOG 0 — 22 1 — 12 2 — 0 3 — 0 unknown — 0
Other	Not Collected
Cancer Types or Histologic Subtypes	Colorectal cancer, adenocarcinoma 34

Primary Assessment Method

Experimental Arm: Colorectal Cancer, Adenocarcinoma

Number of patients screened	34
Number of patients enrolled	34
Number of patients evaluable for toxicity	34
Number of patients evaluated for efficacy	34
Evaluation method	Other
Response assessment CR	0%
Response assessment PR	18.1%
Response assessment SD	72.7%
Response assessment PD	9%
Response assessment other	0%
(Median) duration assessments PFS	240 days, CI: 179-311
(Median) duration assessments OS	665 days, CI: 487-NA



Waterfall plot. Waterfall plot of best response.

Experimental Arm:	Total Patient Population
Evaluation method:	Other
Secondary Assessment Method	
Experimental Arm:	Colorectal Cancer, Adenocarcinoma

Adverse events

Name	*NC/NA	1	2	3	4	5	All grades
Leukocytes (total WBC)	41%	23%	35%	0%	0%	0%	58%
Neutrophils/granulocytes (ANC/AGC)	44%	8%	35%	11%	0%	0%	55%
Hemoglobin	29%	50%	17%	2%	0%	0%	70%
Platelets	52%	41%	5%	0%	0%	0%	47%
Diarrhea	50%	14%	29%	5%	0%	0%	50%
Anorexia	47%	32%	14%	5%	0%	0%	52%
Nausea	47%	32%	11%	8%	0%	0%	52%
Vomiting	70%	20%	5%	2%	0%	0%	29%
Fatigue (asthenia, lethargy, malaise)	61%	11%	23%	2%	0%	0%	38%
Mucositis/stomatitis (clinical exam)	82%	11%	5%	0%	0%	0%	17%
Dizziness	94%	0%	0%	5%	0%	0%	5%
Neuropathy: sensory	70%	17%	8%	2%	0%	0%	29%
Hair loss/alopecia (scalp or body)	67%	17%	14%	0%	0%	0%	32%
Rash: hand-foot skin reaction	38%	44%	11%	5%	0%	0%	61%
Renal/genitourinary, other	52%	20%	23%	2%	0%	0%	47%
Hypertension	67%	5%	17%	8%	0%	0%	32%

*No Change From Baseline/No Adverse Event
Adverse events during phase I/II treatment; no serious adverse events were reported.
Abbreviations: AGC, absolute granulocyte count; ANC, absolute neutrophil count; WBC, white blood cells.

Assessment, Analysis, and Discussion

Completion	Study completed
Pharmacokinetics / Pharmacodynamics	Not collected
Investigator's Assessment	Active and should be pursued further

Discussion

This study was conducted as a second-line treatment with bevacizumab beyond progression. Key eligibility comprised disease progression during or after first-line chemotherapy, including oxaliplatin-based regimens with bevacizumab, and a wild type or *6 or *28 heterozygous genotype for UGT1A1.

Although grade 3 diarrhea was observed in only 5% of patients in our study (Table 1), it was noted that the response rate (18.1%) and progression-free survival (PFS; 8 months) were better than historical second-line data (Figs. 1, 2, 3) [11–13]. In oxaliplatin-refractory second-line treatments without molecular-targeting agents, PFS was ∼2.5–4 months with response rates ＜5%. Compared with second-line trials without bevacizumab, our marked prolongation of PFS could be related to the addition of bevacizumab beyond progression [14–16]. The potential effect of racial differences on tolerability for capecitabine in the east Asian population should be also considered [17]. These advantages would be vital for beyond-progression strategies.

The XELIRI regimen requires only 1 visit per 3-week cycle for a 2- or 3-hour infusion, which may provide a marked advantage over the FOLFIRI regimen in terms of convenience for both patients and clinical staff. XELIRI plus bevacizumab should be considered as a possible standard second-line treatment for Japanese patients with metastatic colorectal cancer. A phase III trial randomizing XELIRI plus bevacizumab versus FOLFIRI plus bevacizumab began in October 2013.

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Figures and Tables

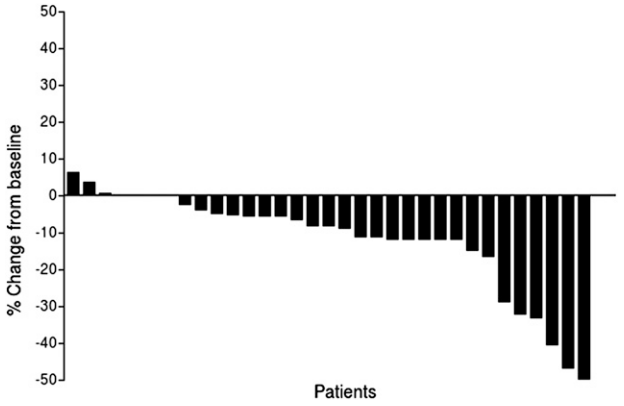

Figure 1. Waterfall plot.

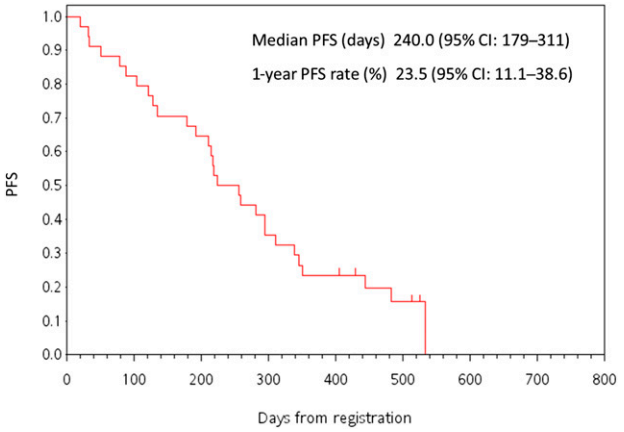

Figure 2. Progression-free survival.
Abbreviations: CI, confidence interval; PFS, progression-free survival.

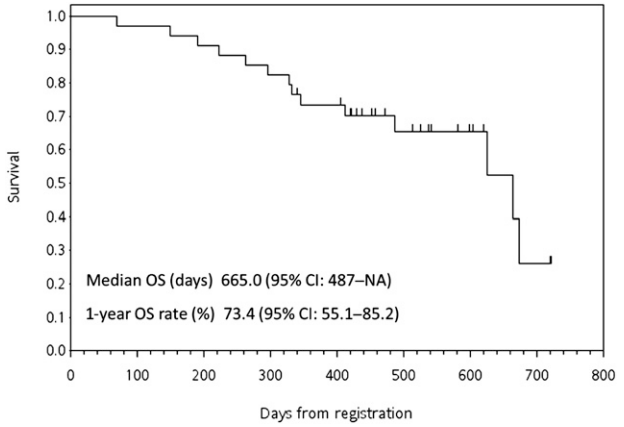

Figure 3. Survival.
Abbreviations: CI, confidence interval; NA, not available; OS, overall survival.

Table 1. Adverse events

Name	*NC/NA	1	2	3	4	5	All grades
Leukocytes (total WBC)	41%	23%	35%	0%	0%	0%	58%
Neutrophils/granulocytes (ANC/AGC)	44%	8%	35%	11%	0%	0%	55%
Hemoglobin	29%	50%	17%	2%	0%	0%	70%
Platelets	52%	41%	5%	0%	0%	0%	47%
Diarrhea	50%	14%	29%	5%	0%	0%	50%
Anorexia	47%	32%	14%	5%	0%	0%	52%
Nausea	47%	32%	11%	8%	0%	0%	52%
Vomiting	70%	20%	5%	2%	0%	0%	29%
Fatigue (asthenia, lethargy, malaise)	61%	11%	23%	2%	0%	0%	38%
Mucositis/stomatitis (clinical exam)	82%	11%	5%	0%	0%	0%	17%
Dizziness	94%	0%	0%	5%	0%	0%	5%
Neuropathy: sensory	70%	17%	8%	2%	0%	0%	29%
Hair loss/alopecia (scalp or body)	67%	17%	14%	0%	0%	0%	32%
Rash: hand-foot skin reaction	38%	44%	11%	5%	0%	0%	61%
Renal/genitourinary, other	52%	20%	23%	2%	0%	0%	47%
Hypertension	67%	5%	17%	8%	0%	0%	32%

*No Change From Baseline/No Adverse Event
Adverse events during phase I/II treatment; no serious adverse events were reported.
Abbreviations: AGC, absolute granulocyte count; ANC, absolute neutrophil count; WBC, white blood cells.

Table 2. Baseline patient characteristics

Characteristics	Phase I ($n = 6$)	Phase I/II ($n = 34$)
Age, years, median (range)	64 (57–72)	60 (22–74)
Sex		
Male	4	24
Female	2	10
Primary tumor site		
Colon	4	21
Rectum	2	13
ECOG PS		
0	4	22
1	2	12
UGTIA1		
Wild type	3	21
*6 Heterozygous	3	7
*28 Heterozygous	0	6
Resection of primary tumor, yes	5	32
Metastatic site		
Liver	3	20
Lung	4	22
Lymph nodes	2	7
Peritoneum	0	4
Other	2	5
Initial treatments		
Regimen		
FOLFOX4 plus bevacizumab	0	1
mFOLFOX6 plus bevacizumab	2	15
XELOX plus bevacizumab	2	10
Other[a]	2	8

Treatment duration, days, median (range)	183 (118–360)	238 (69–1621)
Best overall response		
Complete response	0	1
Partial response	1	17
Stable disease	4	12
Progressive disease	0	2
Not evaluable	1	2
Reasons for termination		
Progression	6	33
Surgery	0	1

[a]Six patients received S-1 plus oxaliplatin plus bevacizumab; 2 patients received S-1/LV plus oxaliplatin plus bevacizumab.
Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; mFOLFOX6, modified FOLFOX6 regimen.

Table 3. Dose intensity of chemotherapy with capecitabine and irinotecan plus bevacizumab

Relative dose intensity	Irinotecan	Capecitabine	Bevacizumab[a]
Mean (95% confidence interval)	91.30 (66.1–116.6)	89.40 (58.5–120.4)	96.30 (77.3–115.3)
Median (range)	100 (47.9–100)	100 (30.0–100)	100 (50.0–100)
Full dose, *n/n*	20/34	20/34	33/34

[a]Bevacizumab: fixed dose (7.5 mg/kg).
Data shown are percentages unless otherwise specified.

Table 4. Adverse events during phase I/II treatment

	Grade, CTCAE version 3.0 ($n = 34$), *n*					
Adverse event	**1**	**2**	**3**	**4**	**All (%)**	**Grade ≥3 (%)**
Leucopenia	8	12	0	0	58.8	0
Neutropenia	3	12	4	0	55.9	11.8
Anemia	17	6	1	0	70.6	2.9
Thrombocytopenia	14	2	0	0	47.1	0
Diarrhea	5	10	2	0	50	5.9
Anorexia	11	5	2	0	52.9	5.9
Nausea	11	4	3	0	52.9	8.8
Vomiting	7	2	1	0	29.4	2.9
Fatigue	4	8	1	0	38.2	2.9
Stomatitis	4	2	0	0	17.6	0
Dizziness	0	0	2	0	5.9	5.9
Neuropathy	6	3	1	0	29.4	2.9
Alopecia	6	5	0	0	32.4	0
Hand-foot syndrome	15	4	2	—	61.8	5.9
Proteinuria	7	8	1	0	47.1	2.9
Hypertension	2	6	3	0	32.4	8.8
Bleeding	2	1	0	0	8.8	0

Median number of cycles: 9 (range: 1–21). No serious adverse events were observed.
Abbreviations: —, no data; CTCAE, Common Terminology Criteria for Adverse Events.

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