ANTICANCER RESEARCH *41*: 5147-5155 (2021)
doi:10.21873/anticanres.15332

Second-line Chemotherapy for Previously Treated Metastatic Small Bowel Adenocarcinoma: A Retrospective Analysis

TAIKO NAKAZAWA[1], YUKIYA NARITA[1], RYOSUKE KUMANISHI[1], TAKATSUGU OGATA[1], YUKI MATSUBARA[1], KAZUKI NOZAWA[1], KYOKO KATO[1], KAZUNORI HONDA[1], TOSHIKI MASUISHI[1], HIDEAKI BANDO[1], SHIGENORI KADOWAKI[1], MASASHI ANDO[1], KAZUO HARA[2], MASAHIRO TAJIKA[3] and KEI MURO[1]

[1]*Department of Clinical Oncology, Aichi Cancer Center Hospital, Nagoya, Japan;*
[2]*Department of Gastroenterology, Aichi Cancer Center Hospital, Nagoya, Japan;*
[3]*Department of Endoscopy, Aichi Cancer Center Hospital, Nagoya, Japan*

Abstract. *Background/Aim: Metastatic small bowel adenocarcinoma (SBA) is a rare disease with poor prognosis. This study aimed to explore the efficacy and safety of second-line chemotherapy for patients with SBA. Patients and Methods: We retrospectively reviewed the clinical characteristics of 27 metastatic patients with SBA after progression on first-line chemotherapy. The patients were divided into Cohort A, receiving second-line chemotherapy, and Cohort B, receiving best supportive care. Results: Patients in Cohort B had higher age, worse performance status, and higher neutrophil-to-lymphocyte ratio compared with those in Cohort A. Cohort A showed significantly better overall survival (OS) compared with Cohort B (median OS, 15.6 vs. 3.4 months; p=0.002). Objective response rate, disease control rate, and median progression-free survival (PFS) for Cohort A were 7%, 74%, and 5.0 months, respectively. Patients who underwent irinotecan-based chemotherapy showed longer PFS and OS compared with those who underwent taxane-based chemotherapy. No significant adverse events were reported. Conclusion: Second-line chemotherapy for metastatic SBA demonstrated clinical activity with acceptable toxicities.*

Small bowel adenocarcinoma (SBA) is considered a rare disease that accounts for 3% of all gastrointestinal malignant tumors and 0.5% of all types of cancer (1). SBA affects men and women almost equally with an incidence of 7.3 cases per 1,000,000 worldwide (2-4). SBA occurs most frequently in the duodenum (45%), whereas 35% of the cases arise in the jejunum, and 20% in the ileum. Because of its rarity, heterogenous clinical presentation, and nonspecific symptoms, SBA is often diagnosed at an advanced stage (5, 6) and is associated with a poor treatment outcome.

To date, no randomized studies have been conducted to demonstrate a benefit of systemic chemotherapy in patients with metastatic SBA, although recently, several small phase II trials of systemic chemotherapy for SBA have evaluated first-line chemotherapy. These studies revealed that progression-free survival (PFS) and overall survival (OS) from the initiation of first-line chemotherapy for metastatic SBA ranged from 5.9 to 11.3 months and from 12.9 to 20.4 months, respectively (7-9). On the basis of these results, several systemic therapy regimens have been recommended to treat metastatic SBA as first-line regimens worldwide. A small phase II trial evaluating second-line chemotherapy for metastatic SBA included 13 patients and showed the efficacy of nab-paclitaxel therapy with an overall response rate (ORR) of 20%, median PFS of 3.2 months, and median OS of 10.9 months (10). Retrospective studies evaluating the FOLFIRI regimen resulted in an ORR of 20%, median PFS of 3.2 months, and median OS of 10.5 months (11). On the basis of these data, taxane-based chemotherapy or FOLFIRI is recommended as a treatment option for second-line or subsequent therapy of metastatic SBA in the National Comprehensive Cancer Network (NCCN) guidelines for SBA (12).

Pembrolizumab therapy is also an important treatment option for patients with solid tumor containing high microsatellite instability (MSI-H) (13). A phase II trial including 19 patients with SBA demonstrated an ORR of 42.1% in patients with MSI-H who received pembrolizumab

Correspondence to: Yukiya Narita, Department of Clinical Oncology, Aichi Cancer Center Hospital, 1-1 Kanokoden, Chikusa-ku, Nagoya, Aichi, 464–8681, Japan. Tel: +81 52762611, Fax: +81 527649855, e-mail: yukiya.narita@aichi-cc.jp

Key Words: Adenocarcinoma, chemotherapy, microsatellite instability, second-line treatment, small bowel cancer.

therapy (13). Although bevacizumab-containing chemotherapy has been suggested to have additional therapeutic effects as first-line treatment in several retrospective studies (14, 15), the addition of targeted drugs has been very limited. The aim of this study was to explore the efficacy and safety of second-line chemotherapy for metastatic SBA patients.

Patients and Methods

Patients. Patients with recurrent or unresectable SBA (metastatic and/or locally advanced SBA) who received second-line chemotherapy or best supportive care (BSC) after progression on first-line chemotherapy at Aichi Cancer Center Hospital were enrolled from January 2011 to October 2019. The selection criteria were as follows: 1) histologically proven adenocarcinoma of the duodenum, jejunum, or ileum, excluding ampullary carcinoma; 2) adjuvant chemotherapy with recurrence during or within 6 months of the last dose that is considered first-line treatment; and 3) adequate bone marrow, hepatic, and renal function. This study was approved by the Institutional Review Board at Aichi Cancer Center Hospital (IRB reference No.: 2019-1-314). Written informed consent for clinical treatment was obtained from all patients.

Treatment. The patients were divided into two cohorts: Cohort A consisted of patients who received second-line chemotherapy, whereas Cohort B included patients who received best supportive care (BSC). The chemotherapeutic regimens for Cohort A were as follows: IRI group, irinotecan-based regimens; TAX group, taxane-based regimens; and Others group, without irinotecan or taxane.

IRI group. The chemotherapy regimens for the IRI group were as follows: 1) Irinotecan alone: irinotecan 150 mg/m^2 on day 1, repeated every 2 weeks; 2) Combination of irinotecan and bevacizumab: irinotecan 150 mg/m^2 and bevacizumab 5 mg/kg on day 1, repeated every 2 weeks; 3) 5-Fluorouracil (FU) + *l*-leucovorin (l-LV) + irinotecan (FOLFIRI): *l*-LV 200 mg/m^2, irinotecan 150 mg/m^2, and bolus 5-FU 400 mg/m^2, followed by infusion of 5-FU 2,400 mg/m^2 for 46 h, repeated every 2 weeks; 4) FOLFIRI + bevacizumab: FOLFIRI and bevacizumab 5 mg/kg, repeated every 2 weeks; 5) FOLFIRI + cetuximab: FOLFIRI and cetuximab 400 mg/m^2 on day 1, then repeated 250 mg/m^2 every week; 6) FOLFIRI + panitumumab: FOLFIRI and panitumumab 6 mg/kg on day 1, then repeated every 2 weeks; 7) Combination of irinotecan and tegafur/gimeracil/oteracil potassium (S-1): S-1 80 mg/m^2 per day orally on days 1-14 and irinotecan 150 mg/m^2 on days 1 and 15, repeated every 4 weeks.

TAX group. The chemotherapy regimens for the TAX group were as follows: 1) Paclitaxel alone: paclitaxel 80 mg/m^2 on days 1, 8, and 15, repeated every 4 weeks; 2) Docetaxel alone: docetaxel 60 mg/m^2 on day 1, repeated every 3 weeks; 3) Combination of nab-paclitaxel and gemcitabine: nab-paclitaxel 125 mg/m^2 and gemcitabine 1,000 mg/m^2 on days 1, 8, and 15, repeated every 4 weeks.

Others group. The chemotherapy regimens for the others group were as follows:1) 5-FU + *l*-LV + oxaliplatin (Modified FOLFOX6): *l*-LV 200 mg/m^2, oxaliplatin 85 mg/m^2, and bolus 5-FU 400 mg/m^2, followed by infusion of 5-FU 2,400 mg/m^2 for 46 h, repeated every 2 weeks; 2) Nivolumab: nivolumab 240 mg on day 1, repeated every 2 weeks.

These treatments were generally repeated until the occurrence of disease progression, appearance of unacceptable toxicities, or the patient's refusal to continue treatment.

Evaluation of treatment and statistical analysis. The patients were divided into Cohort A and Cohort B to evaluate survival outcome. In addition, the patients in Cohort A were divided into two groups according to second-line chemotherapy regimen (IRI group or TAX group) to evaluate treatment outcome. Clinicopathological data were analyzed using the χ^2 test or Fisher's exact test. Tumor response was assessed in patients with measurable lesions using computed tomography scans according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. The response rate was defined as the proportion of patients with a complete response (CR) or partial response (PR) among patients with measurable lesions. Disease control rate (DCR) comprised CR, PR, and stable disease (SD). PFS was defined from the date of the first dose of second-line chemotherapy to the first objective documentation of radiographic progression or death from any cause in Cohort A. OS was defined from the date of disease progression following first-line chemotherapy to the date of death from any cause or the date of the last follow-up. Median PFS and OS were estimated using the Kaplan–Meier method. The log-rank test was used to compare survival rates between groups. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using Cox proportional hazard models. Adjusted HRs for PFS or OS were analyzed by applying univariate and multivariate Cox proportional models based on the factor (*p*-values <0.1) in univariate analysis. For the multivariate analyses for PFS and OS, the following variables were included: age (<65 *vs.* ≥65 years), sex (male *vs.* female), Eastern Cooperative Oncology Group Scale of Performance Status (ECOG PS) (0 or 1 *vs.* ≥2), primary site (duodenum *vs.* jejunum or ileum), histological type (undifferentiated *vs.* differentiated), disease status (unresectable *vs.* recurrent), metastatic sites, number of metastatic sites (1 or 2 *vs.* ≥3), presence of ascites (yes *vs.* no), resection of primary tumor (yes *vs.* no), baseline serum alkali-phosphatase (ALP) level (<380 *vs.* ≥380 U/l), lactate dehydrogenase (LDH) level (<240 *vs.* ≥240 U/l), carcinoembryonic antigen (CEA) level (<5 *vs.* ≥5 ng/ml), carbohydrate antigen 19-9 (CA19-9) level (<37 *vs.* ≥37 U/ml), Glasgow Prognostic Score (GPS) (0 *vs.* 1 or 2), and neutrophil-to-lymphocyte ratio (NLR) (≤4 *vs.* 4<). GPS was calculated as follows: the presence of both elevated c-reactive protein (CRP) (>1.0 mg/dl) and hypoalbuminemia (<3.5 g/dl) levels was awarded a score of 2, the presence of only one of these abnormalities was awarded a score of 1, and the presence of neither of these was scored as 0 (16). NLR was calculated as the ratio of the number of neutrophils to the number of lymphocytes. Mismatch repair (MMR) status was determined by immunohistochemical analysis of the DNA mismatch repair proteins (MLH1, MSH2, MSH6, and PMS2) and was classified as MMR-deficient (dMMR) if any of the MMR proteins was lacking. MSI-H status was determined using the MSI test kit (FALCO) (FALCO Biosystems, Kyoto, Japan) and polymerase chain reaction-based assays of five tumor microsatellite loci (NR-21, BAT-25, MONO-27, NR-24, and BAT-26). Treatment-related adverse events (TRAEs) were assessed according to the National Cancer Center Institute's Common Toxicity Criteria (CTCAE) version 5.0 (17). Statistical significance was defined as *p*-values <0.05. Statistical analyses were performed

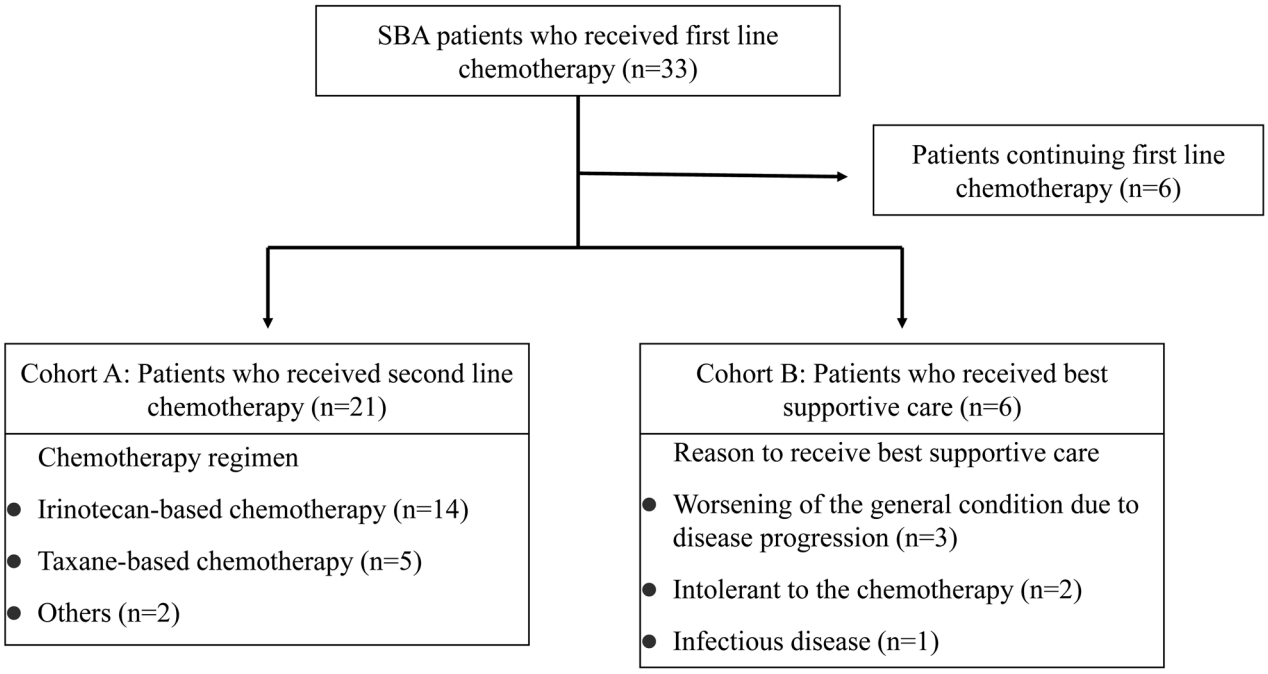

Figure 1. *Study flowchart*.

using EZR statistical software, version 1.53 (Saitama Medical Center, Jichi Medical University, Saitama, Japan).

Results

Patient characteristics. Of the 33 patients with metastatic SBA who received first-line chemotherapy, 27 patients were included in the study. Twenty-one patients were included in Cohort A, and six patients in Cohort B (Figure 1). Baseline characteristics are shown in Table I. The patients in Cohort B were of higher age (median age, 60 *vs*. 67.5 years; p=0.061), worse ECOG PS (ECOG PS more than 2, 5% *vs*. 67%; p=0.0060), and higher NLR (NLR more than 4, 29% and 67%; p=0.15) compared with those in Cohort A. MSI/MMR status was evaluated in eight patients. One patient was MSI-high, and the others were microsatellite stable (MSS) or mismatch repair-proficient (pMMR).

Efficacy. The number of patients with target lesions was 15 in Cohort A. There were no CRs, one patient had a PR (7%), and ten patients had an SD (67%). The ORR was 7%, and the DCR was 74% (Figure 2).

During the median follow-up time of 20.4 months, the median PFS, and median OS from the date of the first dose of second-line chemotherapy were 5.0 (95%CI=2.2-6.1) and 13.9 months (95%CI=5.3-21.8) in Cohort A (Figure 3A). The median OS from the date of disease progression following first-line chemotherapy was 9.4 months (95%CI=3.8-22.2) in the whole population, 15.6 months (95%CI=6.3-22.2) in Cohort A, and 3.3 months (95%CI=1.1-NA) in Cohort B (Figure 3B). The median OS in Cohort A was significantly better compared with that in Cohort B (HR=0.11; 95%CI=0.02-0.52; p<0.001). With respect to the results of the univariate analysis for OS, five factors showed a significant association with worse survival: ECOG PS (HR=4.32; 95%CI=1.05-17.65; p=0.042), NLR (HR=3.60; 95%CI=1.05-12.32; p=0.041), CEA level (HR=3.23; 95%CI=1.05-9.90; p=0.040), CA19-9 level (HR=4.85; 95%CI=1.28-18.26; p=0.020), and exposure to second-line chemotherapy (HR=0.11; 95%CI=0.024-0.52; p=0.0050). Multivariate analysis revealed that CA19-9 level (HR=9.36; 95%CI=1.77-49.47; p=0.0085) and exposure to second-line chemotherapy (HR=0.062; 95%CI=0.0061-0.63; p=0.019) were independent prognostic factors for OS. The six-month PFS rate for Cohort A was 43.8% (95%CI=0.21-0.64). The 1-year survival rates for Cohort A and Cohort B were 60.6% (95%CI=0.34-0.79) and NA (95%CI=NA), respectively.

In Cohort A, 14 patients were treated with regimens of the IRI group; five patients with regimens of the TAX group; and two patients with regimens of the Others group. Differences in patient characteristics were not observed between the IRI group and the TAX group (Table II). The ORR and DCR in the IRI group tended to be higher compared with those in the TAX group (ORR, 10% *vs*. 0%;

Table I. *Patient characteristics*.

		Cohort A (n=21)	%	Cohort B (n=6)	%	*p*-Value
Age (year)	Median (range)	60 (36-77)		67.5 (49-83)		0.061
Gender	Male/Female	12/9	57/43	4/2	67/33	>0.99
ECOG PS	0/1/2/≥3	7/13/1	33/62/5	0/2/4	0/33/67	0.0060
Primary site	Duodenum/Jejunum or ileum	10/11	48/52	3/3	50/50	>0.99
Histology	Differentiated/Undifferentiated	15/6	71/29	5/1	83/17	0.060
Resection of primary tumor	Yes/No	9/12	43/57	4/2	67/33	0.39
Liver Metastasis	Yes/No	9/12	43/57	1/5	17/83	0.36
Lung Metastasis	Yes/No	5/16	24/76	1/5	17/83	>0.99
Peritoneum Metastasis	Yes/No	14/7	67/33	5/1	83/17	0.63
No. of metastatic sites	1/≥2	5/16	24/76	2/4	33/67	0.63
Ascites	Yes/No	9/12	43/57	4/2	67/33	0.39
GPS	0/1 or 2	14/7	67/33	2/4	33/67	0.19
NLR	≤4/>4	15/6	71/29	2/4	33/67	0.15
LDH (U/l)	<240/≥240	14/7	67/33	4/2	67/33	>0.99
MSI/MMR status	MSS or pMMR/MSI-high or dMMR/Unknown	7/1/13	33/5/62	1/0/5	17/0/83	NA
First-line CTx regimen	OX-base/TAX-base/FP + CDDP	19/1/1	90/5/5	5/0/1	83/0/17	NA

ALP: Alkaline phosphatase; BV: bevacizumab; CDDP: cisplatin; CEA: carcinoembryonic antigen; Cmab: cetuximab; CTx: chemotherapy; FP: fluoropyrimidines; GPS: Glasgow prognostic score; LDH: lactate dehydrogenase; MSI: microsatellite instability; MMR: mismatch repair; dMMR: mismatch repair-deficient; MSS: microsatellite stable; pMMR: mismatch repair-proficient; NA: not applicable; NLR: neutrophil–lymphocyte ratio; OX: oxaliplatin; PS: performance status; TAX: taxane.

p=0.64; DCR, 90% *vs*. 50%; *p*=0.14). The median PFS in the IRI group was significantly longer compared with that in the TAX group (HR=4.30; 95% CI=1.13-16.29; median PFS, 7.1 *vs*. 2.5 months; *p*=0.020) (Figure 4A). The median OS of the patients in the IRI group was longer compared with that in the TAX group (HR=0.21; 95%CI=0.06-0.78; median OS, 12.6 *vs*. 5.4 months; *p*=0.020) (Figure 4B).

Seven patients were treated with bevacizumab in the IRI group, resulting in an ORR of 7%, median PFS of 6.1 months (95%CI=1.2-NA), and a median OS of 15.6 months (95%CI=6.3-NA). For the two patients treated with cetuximab or panitumumab combination regimens, ORR was not evaluated (no target lesions). PFS was 5.8 and 38.9 months, and the OS was 19.3 and 65.1 months, respectively. The tumor response in the patient with unknown MSI/MMR status who was treated with nivolumab was considered SD with PFS of 5.1 months and OS of 19.4 months.

In Cohort A, 4 patients continued second-line chemotherapy, 7 patients received BSC, and 11 patients received subsequent treatment. The reasons for the discontinuation of chemotherapy were disease progression in 15 patients, unacceptable adverse events in two patients (one had intracranial hemorrhage because of trauma, and one had anorexia), and patient refusal in one patient.

AEs. The adverse events in Cohort A are summarized in Table III. Any grade of hematological or nonhematological toxicity was observed in 71% and 95% of the patients, respectively. The most common grade 3 or 4 adverse events included neutropenia (43%), anemia (19%), anorexia (10%), and febrile neutropenia (5%). There were no treatment-related deaths, and no patients died within 30 days following the start of second-line chemotherapy.

Discussion

In this single-center, retrospective cohort study, we observed that second-line chemotherapy demonstrated clinical activity and had acceptable toxicity. As a result, we propose three important findings. First, the survival of the patients in the second-line chemotherapy group was significantly longer compared with that of the patients in the BSC group. Second, the patients in the IRI group showed a better prognosis compared with those in the TAX group. Third, the results suggest that molecular-targeted drugs may have a clinical benefit for patients with metastatic SBA.

There have been no reports regarding BSC after progression on first-line chemotherapy, and it is unclear whether the Cohort B results in this study are appropriate. On the other hand, the median OS of Cohort A was relatively longer compared with that of previous studies. These results suggest that patient background related to cancer prognosis may have been better in this study. However, no deaths within 30 days after chemotherapy and no new serious adverse events indicate that chemotherapy as a second-line treatment is feasible and the appropriate patient selection should be weighed in clinical practice. On the basis of the positive results in this study, second-line chemotherapy as a

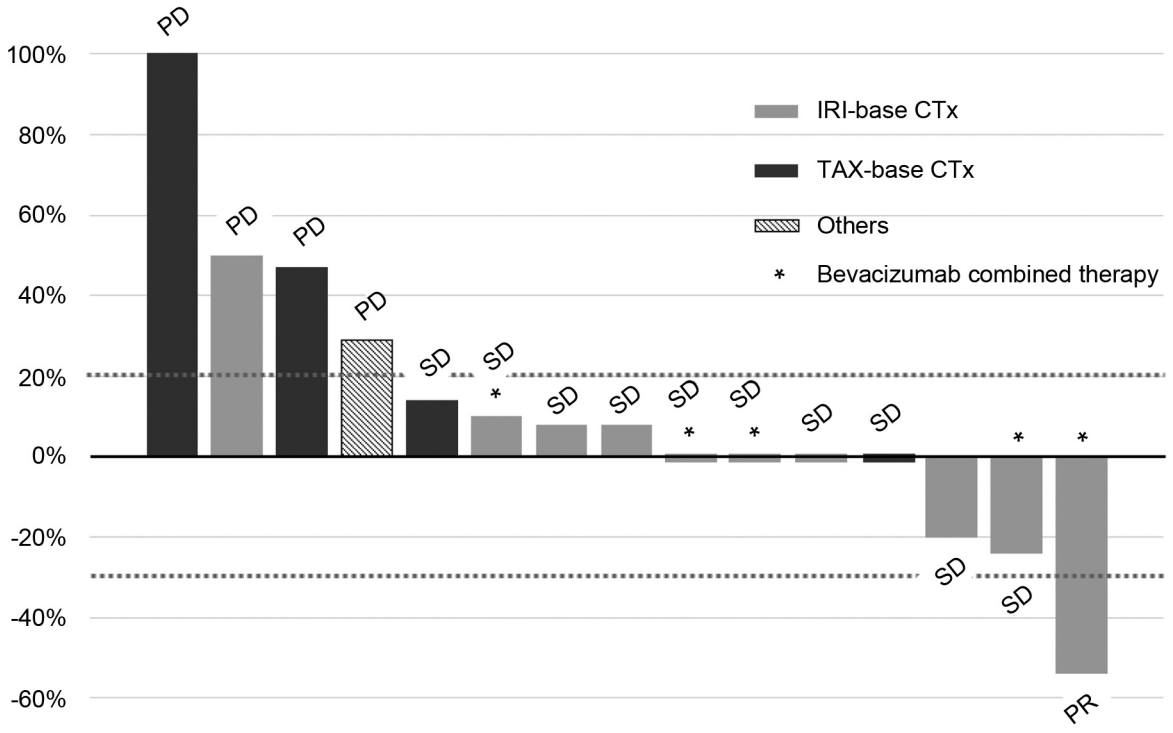

Figure 2. *Waterfall plots showing the best radiographic response of patients in Cohort A with the target region.*

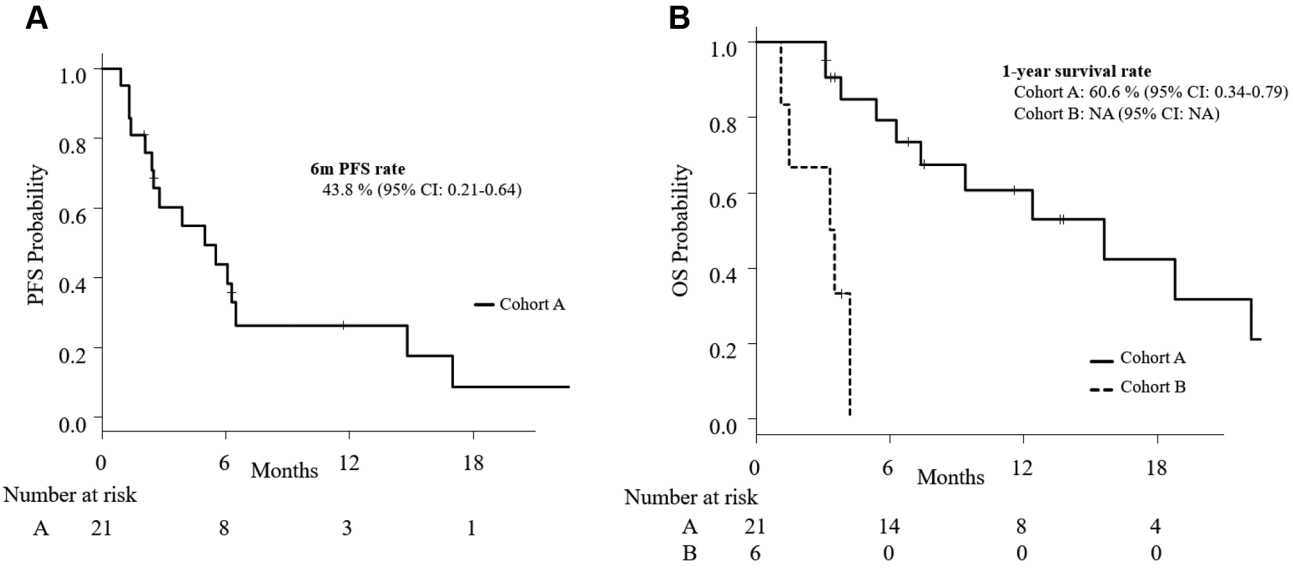

Figure 3. *The rate of progression-free survival (PFS) and overall survival (OS). (A) PFS curve of Cohort A. (B) Overall survival curves for each cohort.*

palliative treatment for patients with SBA is considered an important treatment option.

In previous reports, taxane-based or irinotecan-based regimens were examined as second-line treatment for patients with SBA (10, 11). However, no definitive conclusion was made as to whether it is better to administer irinotecan-based treatment according to colorectal cancer protocols or taxane-based treatment according to gastric cancer protocols. The fact

Table II. *Patient characteristics according to the treatment regimens.*

		IRI-based (n=14)	%	TAX-based (n=5)	%	*p*-Value
Age (year)	Median (range)	62 (36-77)		51 (43-66)		
Gender	Male/Female	6/8	43/57	4/1	80/20	0.18
ECOG PS	0/1/2/≥3	6/7/1	43/50/7	1/4/0	20/80/0	0.56
Primary site	Duodenum/Jejunum or ileum	9/5	64/36	3/2	60/40	0.39
Histology	Differentiated/Undifferentiated	10/4	71/29	3/2	60/40	0.69
Resection of primary tumor	Yes/No	8/6	57/43	1/4	20/80	0.18
Liver Metastasis	Yes/No	7/7	50/50	1/4	20/80	0.28
Lung Metastasis	Yes/No	3/11	21/79	3/2	60/40	0.14
Peritoneum Metastasis	Yes/No	9/5	64/36	4/1	80/20	0.57
No. of metastatic site	1/≥2	5/9	36/64	0/5	0/100	0.15
Ascites	Yes/No	6/8	43/57	3/2	60/40	0.56
GPS	0/1 or 2	11/3	79/21	2/3	40/60	0.14
NLR	≤4/>4	10/4	71/29	3/2	60/40	0.69
LDH (U/l)	<240/≥240	9/5	64/36	4/1	80/20	0.57
MSI/MMR status	MSS or pMMR/MSI-high or dMMR/Unknown	7/0/7	50/0/50	0/0/5	0/0/100	NA
First-line CTx regimen	OX-base/TAX-base/FP + CDDP	14/0/0	100/0/0	4/0/1	80/0/20	NA

GPS: Glasgow prognostic score; LDH: lactate dehydrogenase; NLR: neutrophil–lymphocyte ratio; PS: performance status; MSS: microsatellite stable; TAX: taxane; MSI: microsatellite instability; dMMR: mismatch repair-deficient; pMMR: mismatch repair-proficient; NA: not applicable.

that the patients in the IRI group showed a favorable outcome compared with those in the TAX group may contribute to understanding this clinical question. Although many systemic chemotherapeutic regimens for metastatic SBA are commonly extrapolated from colorectal cancer data, SBA has been reported to have a worse prognosis and is less sensitive to chemotherapy compared with colorectal cancer (18, 19). It has been suggested that these colorectal cancer regimens generally do not work for SBA (7-9). In fact, the genetic background of SBA is different from that of colorectal cancer and gastric cancer. A large study comparing the genetic characteristics of 889 cases of gastric cancer, 6,353 cases of colon cancer, and 317 cases of SBA revealed that SBA had a genetic mutation profile different from that of the other two cancer types. For example, it was reported that the frequencies of APC, SMAD4, and CDKN2A mutations were different from one another (20). Therefore, SBA is considered a disease group that is different from colorectal and gastric cancer.

Molecular-targeted therapy has been shown to be effective, in addition to conventional cytotoxic agents, for the treatment of gastrointestinal cancer (14, 15). In SBA, a small phase 2 trial of panitumumab monotherapy as a second-line treatment was terminated because of no observed clinical effectiveness (21). By contrast, several retrospective studies of first-line treatment have shown the effectiveness of bevacizumab. In this study, patients who were treated with both the combination of anti-VEGF antibody and anti-EGFR antibody with FOLFIRI showed a good clinical outcome. The effectiveness of molecular-targeted drugs may be different depending on the organ. Anti-VEGF and anti-EGFR antibody drugs are known to be effective for colorectal cancer, but other than ramucirumab, they have not been active in gastric cancer (22, 23). There is also a difference in the effect of the anti-EGFR antibody between colorectal cancer in the left side and that in the right side (24-26), suggesting that tumor origin may be related to these effects. The oral side of the duodenum is derived from the foregut, which is the same as the stomach, and the anal side of the duodenum, the jejunum, and the ileum are derived from the midgut, which is the same as the right side of the colon. Therefore, tumor origin may be crucial for the observed therapeutic effects of anti-EGFR and anti-VEGF antibodies in SBA. However, other factors related to the therapeutic effects of molecular-targeted therapies have not been defined, and further investigations for the combined use of molecular-targeted therapy for SBA are warranted.

MSI-H/dMMR and high tumor mutation burden (TMB) have been shown to be effective predictors of immune checkpoint inhibitor activity. One case of unknown MSI/MMR status treated with nivolumab was included in our study and showed a good therapeutic effect. Previous studies have revealed that the frequency of MSI-H and high TMB in SBA are higher compared with those in other gastrointestinal cancers (20). In this study, MSI-H/dMMR screening was performed in only 33% of the patient population, and TMB was not examined. Although all SBA patients may not benefit from immune checkpoint inhibitor treatment, it is important to perform screening and not to overlook the MSI-H/dMMR cases.

There are some limitations of this study. First, this is a retrospective study of a small number of patients at a single

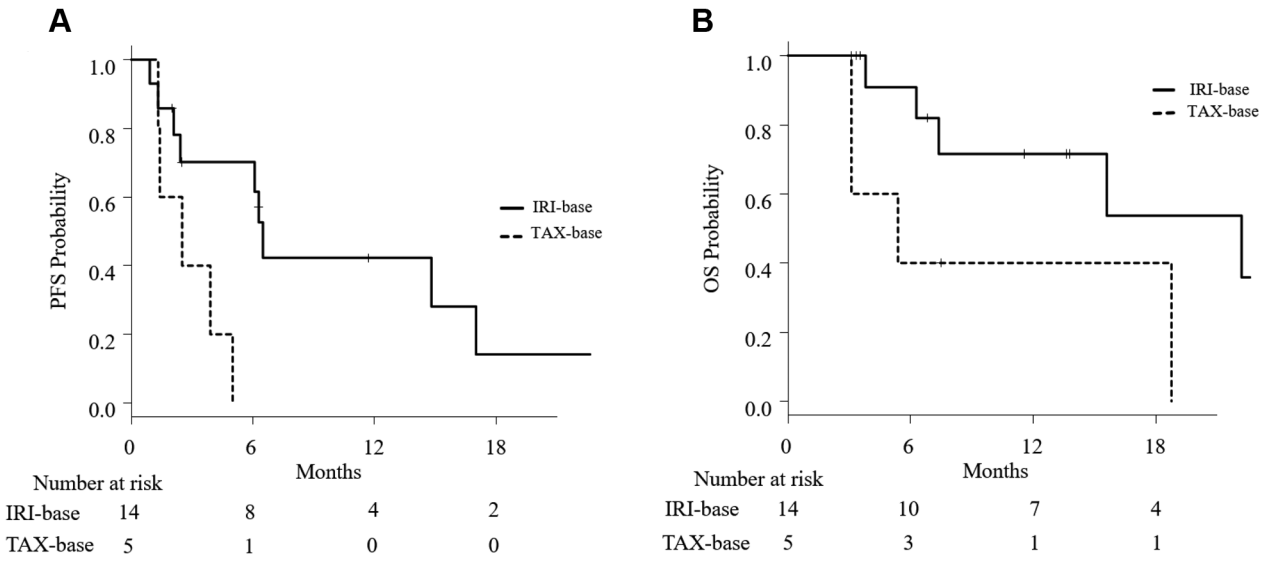

Figure 4. *Progression free survival (PFS) and overall survival (OS) according to treatment regimen. (A) PFS curve of Cohort A stratified by treatment regimen. (B) Overall survival curve of Cohort A stratified by treatment regimen.*

institution. However, because SBA is a rare cancer, it is difficult to conduct a prospective study and even retrospective studies are considered to provide important evidence. As shown in this study, the rate of transition to treatment after progression on second-line therapy is low, so it is especially important to consider second-line treatment. A second limitation is that there may also be a bias in the choice of treatment. Patients who did not receive chemotherapy as second-line treatment exhibited poor prognosis factors, such as worse PS and higher age. Lastly, we could not make a sufficient comparison for each taxane- and irinotecan-based regimen, but the results suggest that prognosis differs depending on the particular regimen. Therefore, we are planning to collect and analyze data from more cases at multiple centers in the future. Moreover, an ongoing randomized phase II trial comparing FOLFIRI with PTX plus ramucirumab will provide further insight into this issue (NCT 04205968).

Conclusion

Our study demonstrated that second-line treatment for metastatic SBA improves prognosis and has a favorable safety profile. The results suggest that the therapeutic effect of irinotecan-based regimens was superior to that of taxane-based regimens for second-line chemotherapy and the combination of molecular-targeted therapy may yield improved clinical efficacy. Our results support the initiation of additional clinical trials to evaluate second-line treatment regimens for metastatic SBA.

Table III. *Adverse events (Cohort A).*

	Any grade	%	Grade ≥3	%
Hematological toxicity				
White blood cell decreased	13	61.9	8	38.1
Neutropenia	13	61.9	9	42.9
Thrombocytopenia	5	23.8	1	4.8
Anemia	14	66.7	4	19.0
Increased AST	8	38.1	0	0
Increased ALT	4	19.0	0	0
Nonhematological toxicity				
Anorexia	12	57.1	2	9.5
Fatigue	19	90.5	0	0
Nausea	9	42.9	0	0
Neuropathy	5	23.8	0	0
Constipation	15	71.4	0	0
Abdominal pain	4	19.0	0	0
Diarrhea	9	42.9	0	0
Rash	3	14.3	0	0
Febrile neutropenia	1	4.8	0	0

ALT: Alanine aminotransferase; AST: aspartate aminotransferase.

Conflicts of Interest

The Authors declare the following conflicts of interest: Yukiya Narita reports grants and personal fees from Ono Pharmaceutical Co., Ltd., and Bristol-Myers Squibb, grants from Astra Zeneca, personal fees from Eli Lilly, Yakult Honsha, Daiichi Sankyo and Taiho, outside the submitted work; Toshiki Masuishi reports grants and personal fees from Ono Pharmaceutical Co., Ltd., grants from

MSD, Daiichi Sankyo and Novartis, personal fees from Takeda, Chugai, Merck Bio Pharma, Taiho, Bayer, Eli Lilly Japan, Yakult Honsha, Sanofi and Bristol-Myers Squibb, outside the submitted work; Hideaki Bando reports grants from Astra Zeneca, personal fees from Taiho and Eli Lilly Japan, outside the submitted work; Shigenori Kadowaki reports grants and personal fees from Ono Pharmaceutical Co., Ltd., Eli Lilly, Taiho and Chugai, grants from MSD and Nobelpharma, personal fees from Bayer, Bristol-Myers Squibb, Daiichi Sankyo, Yakult, Eisai and Merk KGaA, outside the submitted work; Masahiro Tajika reports personal fees from EA Pharma Co., Ltd., and Olympus, outside the submitted work; Kei Muro reports grants and personal fees from Astellas Amgen Biopharma, Ono Pharmaceutical Co., Ltd., Sanofi and Taiho, grants from Daiichi Sankyo, Solasia Pharma, Parexel International, Merck Serono, Pfizer and MSD, personal fees from Astra Zeneca, Bayer, Eli Lilly, Takeda, Bristol-Myers Squibb and Chugai, outside the submitted work; others have declared no potential conflicts of interest in relation to this study.

Authors' Contributions

Taiko Nakazawa and Yukiya Narita generated and edited the figures and wrote the manuscript. The manuscript was reviewed by all Authors. All Authors read and approved the final version of the manuscript.

Acknowledgements

The Authors would like to thank Enago (www.enago.jp) for English language editing and all patients who participated in this study and their families.

References

1 Siegel RL, Miller KD and Jemal A: Cancer statistics, 2019. CA Cancer J Clin *69(1)*: 7-34, 2019. PMID: 30620402. DOI: 10.3322/caac.21551

2 Noone A, Howlader N and Krapcho M: SEER Cancer Statistics Review, 1975-2015, based on November 2017 SEER data submission, posted to the SEER web site, April 2018, 2018. Available at: https://seer.cancer.gov/ [Last accessed on August 31, 2021]

3 Bilimoria KY, Bentrem DJ, Wayne JD, Ko CY, Bennett CL and Talamonti MS: Small bowel cancer in the United States: changes in epidemiology, treatment, and survival over the last 20 years. Ann Surg *249(1)*: 63-71, 2009. PMID: 19106677. DOI: 10.1097/SLA.0b013e31818e4641

4 Lu Y, Fröbom R and Lagergren J: Incidence patterns of small bowel cancer in a population-based study in Sweden: increase in duodenal adenocarcinoma. Cancer Epidemiol *36(3)*: e158-e163, 2012. PMID: 22405637. DOI: 10.1016/j.canep.2012.01.008

5 Overman MJ, Hu CY, Kopetz S, Abbruzzese JL, Wolff RA and Chang GJ: A population-based comparison of adenocarcinoma of the large and small intestine: insights into a rare disease. Ann Surg Oncol *19(5)*: 1439-1445, 2012. PMID: 22187121. DOI: 10.1245/s10434-011-2173-6

6 Lepage C, Bouvier AM, Manfredi S, Dancourt V and Faivre J: Incidence and management of primary malignant small bowel cancers: a well-defined French population study. Am J Gastroenterol *101(12)*: 2826-2832, 2006. PMID: 17026561. DOI: 10.1111/j.1572-0241.2006.00854.x

7 Gulhati P, Raghav K, Shroff RT, Varadhachary GR, Kopetz S, Javle M, Qiao W, Wang H, Morris J, Wolff RA and Overman MJ: Bevacizumab combined with capecitabine and oxaliplatin in patients with advanced adenocarcinoma of the small bowel or ampulla of vater: A single-center, open-label, phase 2 study. Cancer *123(6)*: 1011-1017, 2017. PMID: 27859010. DOI: 10.1002/cncr.30445

8 Horimatsu T, Nakayama N, Moriwaki T, Hirashima Y, Fujita M, Asayama M, Moriyama I, Nakashima K, Baba E, Kitamura H, Tamura T, Hosokawa A, Yoshimura K and Muto M: A phase II study of 5-fluorouracil/L-leucovorin/oxaliplatin (mFOLFOX6) in Japanese patients with metastatic or unresectable small bowel adenocarcinoma. Int J Clin Oncol *22(5)*: 905-912, 2017. PMID: 28536826. DOI: 10.1007/s10147-017-1138-6

9 Overman MJ, Varadhachary GR, Kopetz S, Adinin R, Lin E, Morris JS, Eng C, Abbruzzese JL and Wolff RA: Phase II study of capecitabine and oxaliplatin for advanced adenocarcinoma of the small bowel and ampulla of Vater. J Clin Oncol *27(16)*: 2598-2603, 2009. PMID: 19164203. DOI: 10.1200/JCO.2008.19.7145

10 Overman MJ, Adam L, Raghav K, Wang J, Kee B, Fogelman D, Eng C, Vilar E, Shroff R, Dasari A, Wolff R, Morris J, Karunasena E, Pisanic TR 2nd, Azad N and Kopetz S: Phase II study of nab-paclitaxel in refractory small bowel adenocarcinoma and CpG island methylator phenotype (CIMP)-high colorectal cancer. Ann Oncol *29(1)*: 139-144, 2018. PMID: 29069279. DOI: 10.1093/annonc/mdx688

11 Zaanan A, Gauthier M, Malka D, Locher C, Gornet JM, Thirot-Bidault A, Tougeron D, Taïeb J, Bonnetain F, Aparicio T and Association des Gastro Entérologues Oncologues: Second-line chemotherapy with fluorouracil, leucovorin, and irinotecan (FOLFIRI regimen) in patients with advanced small bowel adenocarcinoma after failure of first-line platinum-based chemotherapy: a multicenter AGEO study. Cancer *117(7)*: 1422-1428, 2011. PMID: 21425142. DOI: 10.1002/cncr.25614

12 Benson AB, Venook AP, Al-Hawary MM, Arain MA, Chen YJ, Ciombor KK, Cohen SA, Cooper HS, Deming DA, Garrido-Laguna I, Grem JL, Hoffe SE, Hubbard J, Hunt S, Kamel A, Kirilcuk N, Krishnamurthi S, Messersmith WA, Meyerhardt J, Miller ED, Mulcahy MF, Nurkin S, Overman MJ, Parikh A, Patel H, Pedersen KS, Saltz LB, Schneider C, Shibata D, Skibber JM, Sofocleous CT, Stoffel EM, Stotsky-Himelfarb E, Willett CG, Johnson-Chilla A, Gregory KM and Gurski LA: Small bowel adenocarcinoma, version 1.2020, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw *17(9)*: 1109-1133, 2019. PMID: 31487687. DOI: 10.6004/jnccn.2019.0043

13 Marabelle A, Le DT, Ascierto PA, Di Giacomo AM, De Jesus-Acosta A, Delord JP, Geva R, Gottfried M, Penel N, Hansen AR, Piha-Paul SA, Doi T, Gao B, Chung HC, Lopez-Martin J, Bang YJ, Frommer RS, Shah M, Ghori R, Joe AK, Pruitt SK and Diaz LA Jr: Efficacy of pembrolizumab in patients with noncolorectal high microsatellite instability/mismatch repair-deficient cancer: results from the phase II KEYNOTE-158 study. J Clin Oncol *38(1)*: 1-10, 2020. PMID: 31682550. DOI: 10.1200/JCO.19.02105

14 Takayoshi K, Kusaba H, Uenomachi M, Mitsugi K, Makiyama C, Makiyama A, Uchino K, Shirakawa T, Shibata Y, Shinohara Y, Inadomi K, Tsuchihashi K, Arita S, Ariyama H, Esaki T, Akashi K and Baba E: Suggestion of added value by bevacizumab to chemotherapy in patients with unresectable or recurrent small

bowel cancer. Cancer Chemother Pharmacol *80(2)*: 333-342, 2017. PMID: 28653251. DOI: 10.1007/s00280-017-3371-0

15 Legué LM, van Erning FN, Bernards N, Lemmens VEPP, de Hingh IHJT and Creemers GJ: Addition of bevacizumab to first-line palliative chemotherapy in patients with metastatic small bowel adenocarcinoma: a population-based study. Target Oncol *14(6)*: 699-705, 2019. PMID: 31625001. DOI: 10.1007/s11523-019-00681-1

16 McMillan DC, Crozier JE, Canna K, Angerson WJ and McArdle CS: Evaluation of an inflammation-based prognostic score (GPS) in patients undergoing resection for colon and rectal cancer. Int J Colorectal Dis *22(8)*: 881-886, 2007. PMID: 17245566. DOI: 10.1007/s00384-006-0259-6

17 Common Terminology Criteria for Adverse Events (CTCAE). Available at: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm [Las accessed on August 31, 2021]

18 Halfdanarson TR, McWilliams RR, Donohue JH and Quevedo JF: A single-institution experience with 491 cases of small bowel adenocarcinoma. Am J Surg *199(6)*: 797-803, 2010. PMID: 20609724. DOI: 10.1016/j.amjsurg.2009.05.037

19 Dabaja BS, Suki D, Pro B, Bonnen M and Ajani J: Adenocarcinoma of the small bowel: presentation, prognostic factors, and outcome of 217 patients. Cancer *101(3)*: 518-526, 2004. PMID: 15274064. DOI: 10.1002/cncr.20404

20 Schrock AB, Devoe CE, McWilliams R, Sun J, Aparicio T, Stephens PJ, Ross JS, Wilson R, Miller VA, Ali SM and Overman MJ: Genomic profiling of small-bowel adenocarcinoma. JAMA Oncol *3(11)*: 1546-1553, 2017. PMID: 28617917. DOI: 10.1001/jamaoncol.2017.1051

21 Gulhati P, Raghav K, Shroff R, Varadhachary G, Javle M, Qiao W, Wang H, Morris J, Wolff R and Overman MJ: Phase II study of panitumumab in RAS wild-type metastatic adenocarcinoma of small bowel or ampulla of vater. Oncologist *23(3)*: 277-e26, 2018. PMID: 29259073. DOI: 10.1634/theoncologist.2017-0568

22 Lordick F, Kang YK, Chung HC, Salman P, Oh SC, Bodoky G, Kurteva G, Volovat C, Moiseyenko VM, Gorbunova V, Park JO, Sawaki A, Celik I, Götte H, Melezínková H, Moehler M and Arbeitsgemeinschaft Internistische Onkologie and EXPAND Investigators: Capecitabine and cisplatin with or without cetuximab for patients with previously untreated advanced gastric cancer (EXPAND): a randomised, open-label phase 3 trial. Lancet Oncol *14(6)*: 490-499, 2013. PMID: 23594786. DOI: 10.1016/S1470-2045(13)70102-5

23 Waddell T, Chau I, Cunningham D, Gonzalez D, Okines AF, Okines C, Wotherspoon A, Saffery C, Middleton G, Wadsley J, Ferry D, Mansoor W, Crosby T, Coxon F, Smith D, Waters J, Iveson T, Falk S, Slater S, Peckitt C and Barbachano Y: Epirubicin, oxaliplatin, and capecitabine with or without panitumumab for patients with previously untreated advanced oesophagogastric cancer (REAL3): a randomised, open-label phase 3 trial. Lancet Oncol *14(6)*: 481-489, 2013. PMID: 23594787. DOI: 10.1016/S1470-2045(13)70096-2

24 Brulé SY, Jonker DJ, Karapetis CS, O'Callaghan CJ, Moore MJ, Wong R, Tebbutt NC, Underhill C, Yip D, Zalcberg JR, Tu D and Goodwin RA: Location of colon cancer (right-sided *versus* left-sided) as a prognostic factor and a predictor of benefit from cetuximab in NCIC CO.17. Eur J Cancer *51(11)*: 1405-1414, 2015. PMID: 25979833. DOI: 10.1016/j.ejca.2015.03.015

25 Peeters M, Price T, Taieb J, Geissler M, Rivera F, Canon JL, Pentheroudakis G, Koukakis R, Burdon P and Siena S: Relationships between tumour response and primary tumour location, and predictors of long-term survival, in patients with RAS wild-type metastatic colorectal cancer receiving first-line panitumumab therapy: retrospective analyses of the PRIME and PEAK clinical trials. Br J Cancer *119(3)*: 303-312, 2018. PMID: 30013091. DOI: 10.1038/s41416-018-0165-z

26 Arnold D, Lueza B, Douillard JY, Peeters M, Lenz HJ, Venook A, Heinemann V, Van Cutsem E, Pignon JP, Tabernero J, Cervantes A and Ciardiello F: Prognostic and predictive value of primary tumour side in patients with RAS wild-type metastatic colorectal cancer treated with chemotherapy and EGFR directed antibodies in six randomized trials. Ann Oncol *28(8)*: 1713-1729, 2017. PMID: 28407110. DOI: 10.1093/annonc/mdx175

Received July 8, 2021
Revised August 5, 2021
Accepted September 1, 2021