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ORIGINAL ARTICLE

Efficacy and safety of cetuximab plus FOLFOX in second-line and third-line therapy in metastatic colorectal cancer

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Summary

Purpose: *To evaluate the efficacy and adverse events with cetuximab plus FOLFOX administered as second- and third-line therapy in metastatic colorectal cancer (mCRC) patients.*

Methods: *IPatients were administered cetuximab plus FOLFOX as second- and third-line therapy from January 2010 through October 2015. mCRC patients with wild type KRAS were also given irinotecan and/or oxaliplatin combined with fluoropyrimidine±bevacizumab. Tumor response and survival were evaluated using RECIST and Kaplan-Meier method respectively.*

Results: *Sixty patients were included this study. Cetuximab plus FOLFOX was administered to 40 (66.7%) patients as second-line and to 20 (33.3%) as third-line therapy. The majority of the patients had a good ECOG performance status (PS) (0 or 1). Clinical benefit was partial plus stable disease and it was 75.0% for both of these two lines. The median progression free survival (PFS) was 7.1 months (95% CI=3.2-10.9) and 6.0 months (95% CI=2.4-9.6), in the second- and third-line (p=0.484). The median overall survival (OS) was 14.3 and 9.2 months in second- and third-line therapy respectively (p=0.071). The common toxicities were haematologic and gastrointestinal, mostly grade 1 and 2.*

Conclusion: *The addition of cetuximab to FOLFOX was well-tolerated and had antitumor activity both in second- and third-line therapy in patients with mCRC.*

Key words: *cetuximab, chemotherapy, colorectal cancer, second line, third line*

Introduction

Multiple lines of treatment can be reasonable for eligible patients with mCRC. Three major chemotherapeutic agents including irinotecan, oxaliplatin and 5-fluorouracil, two antivascular endothelial growth factor agents including aflibercept and bevacizumab, and two epidermal growth factor receptor (EGFR) inhibitors including cetuximab and panitumumab have demonstrated to exert good clinical activity for the treatment of mCRC [1,2].

EGFR is an essential cell growth regulator involved in the pathogenesis and progression of several human malignancies [3]. Biologic targeting of EGFR has shown to consistently present activity in mCRC. The EGFR, which mediates cell proliferation, differentiation, migration and adhesion, is involved in the critical processes of tumor growth and progression such as apoptosis inhibition, angiogenesis, invasiveness, and metastatic

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spread of tumors [4]. A chimeric IgG1 monoclonal antibody, cetuximab, was the first EGFR targeted biologic agent which has approved by the FDA for usage in patients with mCRC [5].

In patients with RAS wild-type mCRC, cetuximab is recommended to be used in combination with standard first-line treatment regimens [1]. Clinical effectiveness of cetuximab has been proven in patients having chemotherapy-refractory wild-type KRAS exon 2 mCRC [6,7]. Because a subset of CRC depends on the activation of EGFR, combined chemotherapy regimens that block anti-EGFR monoclonal antibodies such ascetuximab plus 5-fluorouracil, folinic acid and irinotecan (FOLFIRI) or cetuximab plus 5-fluorouracil, folinic acid and oxaliplatin (FOLFOX) represent a beneficial therapeutic option in these patients [8,9].

With the introduction of targeted agents (anti-VEGFR and anti-EGFR), survival has been markedly prolonged in mCRC. There are numerous studies regarding the use of these agents in the first-line; however, data particularly about the use of anti-EGFR agents in the second- and third-line therapy are scarce in the literature. Recently, a phase II trial has been published about cetuximab plus FOLFOX as second-line treatment [10] whilst there is still no study in the literature about the use of cetuximab plus FOLFOX therapy as third-line therapy. Therefore, we aimed to evaluate the efficacy and adverse events (AE) of cetuximab plus FOLFOX in the second- and third-line therapies.

Methods

Data collected from the Oncology Department of 7 centers were retrospectively reviewed. Patients who were administered infusion of oxaliplatin 85 mg/m^2 over 2 hrs with concurrent administration of leucovorin 400 mg/m^2 followed by 5-fluorouracil 400 mg/m^2 as bolus injection and 5-fluorouracil 2400 mg/m^2 as intravenous infusion over 46 hrs plus cetuximab 500 mg/m^2 as intravenous infusion over 1.5 hrs in the second-line or third-line treatment, were considered eligible for the study. These cycles were repeated once every two weeks. Response evaluation was based on the Response Evaluation Criteria in Solid Tumors (RECIST) with 2-3 months intervals. Progression of disease was monitored through clinical assessment, imaging methods and tumor markers. A total of 60 patients who had been treated with cetuximab plus FOLFOX from January 2010 through October 2015 and had received irinotecan and/or oxaliplatin combined with fluoropyrimidine ± bevacizumab as previous therapy were included in the evaluation. None of the patients had received cetuximab in previous therapy. Toxicity was evaluated according to the Common Toxicity Criteria of the National Cancer Institute (NCI) and the doses were reduced or delayed in cases of AEs, if necessary. In cases of grade 3/4 AEs, chemotherapy dose was decreased by 20%.

Statistics

Statistical analyses were performed using SPSS 22.0 software (IBM,USA). PFS was considered as the duration between initiation of cetuximab plus FOLFOX and radiologic progression or death and was calculated using the Kaplan-Meier method and log rank test was performed to assess differences. To determine the relationship between variables, Pearson's correlation coefficient was used. A p value<0.05 was considered as statistically significant in all calculations.

Results

Patient characteristics

A total of 60 patients treated between January 2010 and October 2015 were included in the study. None of the patients had KRAS mutation at codons 12 and 13. No NRAS mutation analysis was carried out in any patient.

Patient demographics are displayed in Table 1. The median follow-up duration was 34 months during which 48 (80%) patients died. The median age was 55 years (range 27-80), and 58% of the patients were male. Eastern Cooperative Oncology Group (ECOG) performance status (PS) was 0 in 24 (40%) and 1 in 36 (60%) patients. Cetuximab plus FOLFOX therapy was administered to 40 patients as second-line and in 20 patients as third-line therapy. Of the patients administered cetuximab plus FOLFOX as second-line, 35 had previously received bevacizumab plus FOLFIRI and 5 FOLFIRI as first-line therapy. Patients administered cetuximab plus FOLFOX in third-line treatment were those that had received irinotecan and oxaliplatin therapy in the first two lines and rechallenged with oxaliplatin-based chemotherapy. Forty patients (66.7%) had liver metastasis. No statistically significant differences were found in terms of patient characteristics between the second- and third-line cetuximab plus FOLFOX therapy groups (p>0.05).

Efficacy

Of the 60 patients enrolled in the study, 20 (33.3%) achieved partial response to therapy and 25 (41.7%) had stable disease (Table 2). The objective response rate (ORR) was 33.3% and the clinical benefit rate 75.0% in all patients receiving cetuximab plus FOLFOX therapy.

The median PFS was 7.1 months (95% CI=3.2-10.9) in the second-line and 6.0 months (95% CI=2.4-9.6) in the third-line therapy (p=0.484) (Figure 1), whereas the median OS was 14.3 months (95% CI=11.5-17.1) in the second-line and

9.2 months (95% CI=7.0-11.3) in the third-line therapy (p=0.071) (Figure 2).

Safety

Fifty patients (83.3%) withdrew from the cetuximab plus FOLFOX therapy due to progression of disease and 2 patients (3.3%) due to AEs which were acne-like rash. No patient died because of treatment toxicity. All 60 patients experienced at least one AE during therapy, most of which were mild to moderate in severity. The most common grade 3/4 AE with cetuximab plus FOLFOX was neutropenia (36.7%) followed by cutaneous reactions (13.3%) and diarrhoea (10.0%) (Table 3). In cetuximab- (n=18, 30.0%), oxaliplatin- (n=28, 46.6%) and 5-fluorouracil-treated patients (n=32, 53.3%), AEs such as neutropenia, cutaneous reactions, diarrhoea, vomiting, fatigue, neuropathy, hand-foot syndrome and increased transaminases, caused dose modifications. Although AEs were more common in patients administered third-line cetuximab plus FOLFOX, no statistically significant difference was found in terms of AEs between the second- and third-line therapy groups.

Table 1. Comparison of patient and disease characteristics between second-line and third-line FOLFOX plus cetuximab

Characteristics	*FOLFOX + Cetuximab in second-line n (%)*	*FOLFOX + Cetuximab in third-line n (%)*	*Total n (%)*
Gender			
Male	25 (38)	10 (50)	35 (58)
Female	15 (62)	10 (50)	25 42)
Age (years)			
Median	55.5	52	55
Range	27-80	32-75	27-80
Tumor site			
Colon	21 (53)	13 (65)	34 (57)
Rectum	19 (47)	7 (35)	26 (43)
ECOG PS			
0	13 (32)	7 (35)	20 (33)
1	27 (68)	13 (65)	40 (67)
Metastasis			
Liver	30 (75)	14 (70)	44 (73)
Lung	10 ((25)	5 (25)	15 (25)
Other	9 (23)	5 (25)	14 (23)
Number of metastases			
Single	24 (60)	13 (65)	37 (62)
Multiple	16 (40)	7 (35)	23 (38)

No statistically significant differences between second-line and third-line FOLFOX plus cetuximab for patients characteristics (p > 0.05).

FOLFOX: folinic acid, 5-fluorouracil and oxaliplatin

Table 2. Comparison of tumor response rates with FOLFOX +cetuximab in second-line and third-line

*Tumor response**	*FOLFOX + Cetuximab in second-line (n=40)*	*FOLFOX + Cetuximab in third-line (n=20)*	*Total (n=60)*
CR	-	-	-
PR	14	6	20
SD	16	9	25
PD	10	5	15
Response rate (%)	35.0	30.0	33.3
Disease control rate (%)	75.0	75.0	75.0

*No statistically significant differences between second-line and third-line FOLFOX plus cetuximab (p > 0.05) for tumor response rates

FOLFOX: folinic acid, 5-fluorouracil and oxaliplatin, CR: complete regression, PR: partial regression, SD: stable disease, PD: progressive disease

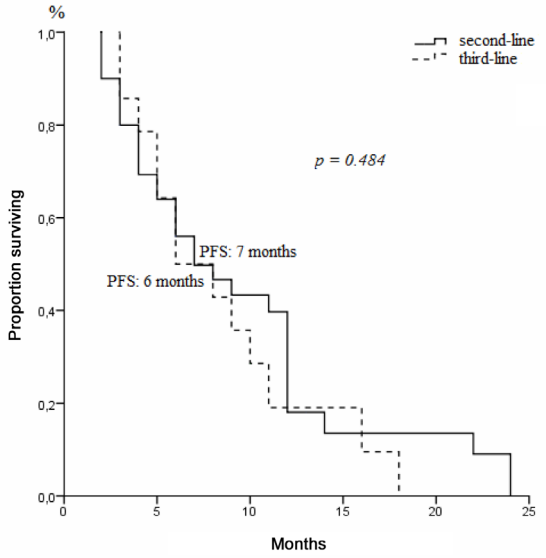

Figure 1. Progression-free survival of cetuximab plus FOLFOX in second- and third-line therapy.

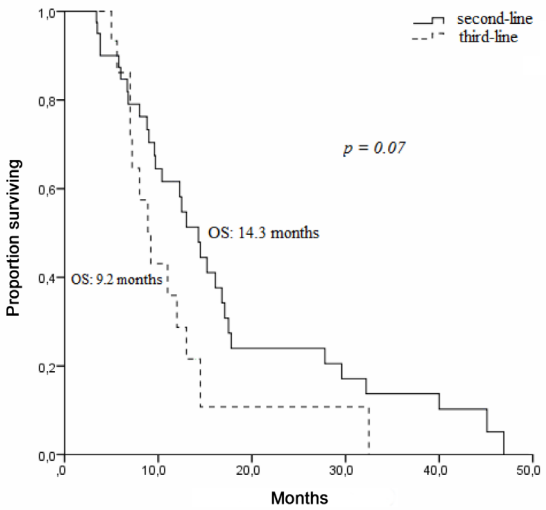

Figure 2. Overall survival of cetuximab plus FOLFOX in second- and third-line therapy.

Table 3. Grade 3 and 4 adverse events in all patients

*Adverse events**	*Second-line chemotherapy*		*Third-line chemotherapy*		*Total*
	Grade 3 (n)	*Grade 4 (n)*	*Grade 3 (n)*	*Grade 4 (n)*	*Grade 3/4 (%)*
Neutropenia	7	6	4	5	36.7
Neuropathy	1	-	1	-	3.3
Diarrhea	3	-	2	1	10.0
Vomiting	3	-	1	-	6.7
Fatigue	2	-	2	-	5.0
AST/ALT increase	1	-	1	-	3.3
Hand-foot syndrome	1	-	1	-	3.3
Cutaneous reactions	4	1	2	1	13.3

*No statistically significant differences between second-line and third-line FOLFOX plus cetuximab for adverse events (p>0.05).
AST: aspartate transaminase, ALT: alanine transaminase

Discussion

Several phase III trials have reported the efficacy of bevacizumab in the first- or second-line treatment of mCRC [11,12], but there are no data in the literature that support its administration beyond the second-line. While anti-EGFR drugs (panitumumab, cetuximab) were shown to exert clinical activity in third-line treatment, these agents are also recommended for the first- and second-line therapy [13,14].

In the present study, the clinical benefit rate was 75.0% in the second-line therapy. Studies have reported clinical benefit rate in 65.8% 10 in patients receiving FOLFOX regimens [10] and 60-65% in patients receiving FOLFIRI regimens as second-line therapy [13,15]. However, objective response rates exceeded 70% (71-85%) when anti-EGFR agents, such as cetuximab or panitumumab, were added to FOLFIRI or FOLFOX in wild-type KRAS patients in the second-line [10,13,14] The present and previous studies [9-14] demonstrated that the clinical benefit rate of chemotherapy plus anti-EGFR was higher compared with chemotherapy alone in the second-line therapy.

In the present study, the median PFS and OS were 7.1 and 14.3 months, respectively, in patients receiving second-line therapy. The effectiveness of second-line cetuximab plus FOLFOX therapy on wild-type KRAS tumors was evaluated in a phase II, randomized, double-arm study performed in patients who had been previously treated with cetuximab plus FOLFOX (CAPRI-GOIM study) [10]. The median PFS and OS were 6.4 and 17.6 months in the group treated with cetuximab plus FOLFOX and 4.5 and 14.0 months in the group administered FOLFOX, respectively. In addition, several authors reported that median PFS and OS were also lower in patients who received only FOLFIRI in the second-line (median PFS, range=3.7-4.7 months [13,15-17]; median OS, range=9.3-12.5 months) [13,15-17]. Thus, addition of cetuximab to FOLFOX or FOLFIRI as second-line therapy provided additional benefit in mCRC patients with wild-type KRAS tumors.

Searching the studies evaluating anti-EGFR plus chemotherapy, except the CAPRI-GOIM study, the efficacy of second-line cetuximab plus FOLFOX was also assessed in a phase II, open-label, single-arm study conducted on patients with wild-type KRAS (FLIER study) [14]. Previous therapies of the patients included bevacizumab plus FOLFOX (n=32;53.3%), FOLFOX alone (n=14;23.3%), cediranib plus FOLFOX or placebo (n=11;18.3%), and others (n=3;5.0%). The results of that study indicated longer PFS (7.4 months) and OS (18.2 months) compared to the findings obtained in our study. In another phase II, open-label, single-arm study (PRECEPT) [18], panitumumab plus FOLFIRI were administered to patients with wild-type KRAS as second-line therapy. In that study, PFS (6.5 months) and OS (12.5 months) were lower in patients with wild-type KRAS mCRC, compared to the findings obtained in our study. Patients in that study had been administered bevacizumab plus oxaliplatin-based chemotherapy in the first-line treatment. High PFS and OS values in our study might be attributed to good performance status of our patients who mostly had a single metastasis.

Efficacy of bevacizumab in the first- or second-line has been reported in phase III trials, but no data were found investigating its application beyond the second-line. While anti-EGFR agents (panitumumab, cetuximab) have proven clinical activity in third-line treatment, these agents are also recommended for the first- and second-line chemotherapy [19]. In case of disease progression after the first- and second-line therapies, survival

has been reported as 4 to 6 months with best supportive care alone [20,21].

In a prospective phase II study investigating the rechallenge of cetuximab plus irinotecan-based chemotherapy, clinical benefit with the same regimen followed by progression was observed in 39 patients who had previously received at least two lines. Promising results were obtained from that study with an objective response rate of 53.8% and a stable disease rate of 35.9%. The median PFS was 6.6 months [11].

The number of studies, particularly about the combination therapy with irinotecan and cetuximab in the third-line therapy, is relatively high in the literature and the median PFS was found between 4.3-5.4 months and OS between 8.9-10.8 months in these studies [23-25]. However, there is yet no study demonstrating the efficacy of oxaliplatin-based therapy with cetuximab in the third-line. In the present study, the median PFS and OS were 6.0 and 9.2 months, respectively, in patients administered third-line therapy. It is noteworthy that no significant difference was found in terms of PFS between the second- and third-line therapies. This may be explained with rechallenging again using oxaliplatin because of the good response achieved with this agent in the first-line, wild-type KRAS patients who had not previously received anti-EGFR treatment, the good performance status of the patients and the high incidence of single-organ metastases. Although regorafenib therapy is an emerging option in the treatment guidelines in the third line in mCRC, cetuximab plus FOLFOX therapy can be said to be a more appropriate treatment in the third line in patients who meet the above mentioned criteria.

In the present study, the most common grade 3/4 therapy-related toxicity was neutropenia (26.7%) and grade 3/4 cetuximab-related cutaneous reactions (13.3%). In a study of second-line cetuximab plus FOLFOX in patients with wild-type KRAS, grade 3/4 AEs were skin-related toxicities (27%) followed by neutropenia (10.9%), fatigue (12.2%), diarrhea (6.8%) and neuropathy (5.4%) [10]. In another study, after the second-line cetuximab plus FOLFIRI, grade 3/4 AEs were skin-related toxicities (25%), neutropenia (43.3%), leukopenia (26.7%), vomiting (5%) and diarrhea (1.7%) [14]. One more study about second-line panitumumab plus FOLFIRI in patients with wild-type KRAS reported grade 3/4 AEs which were neutropenia (23%), skin-related toxicities (28%) and diarrhea (14%) [13]. High rates of neutropenia were found in both of the above mentioned studies as well as in our study, with moderate to severe neutropenia occurring in nearly more than one-third of all patients. Therefore, it may be a reasonable approach to modify chemotherapy doses after the first-line by initially decreasing the doses in selected patients with mCRC.

In conclusion, this study was the first to evaluate the efficacy of cetuximab plus FOLFOX treatment in patients with wild-type KRAS receiving third-line treatment for mCRC. Addition of cetuximab to rechallenged FOLFOX was well-tolerated and had antitumor activity in the second-line as well as the third-line therapy in patients with mCRC who had not previously received anti-EGFR and had a good performance status and sufficient organ function. Despite the small number of patients, this study is valuable since there is only one study [10] conducted so far about cetuximab plus FOLFOX regimen in the second-line treatment in mCRC. Further studies with a larger number of patients are warranted on this subject.

Conflict of interests

The authors declare no confict of interests.

References

1. Van Cutsem E, Cervantes A, Nordlinger B, Arnold D; ESMO Guidelines Working Group. Metastatic colorectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2014;25 (3 Suppl) :iii1-9.
2. Ohhara Y, Fukuda N, Takeuchi S et al. Role of targeted therapy in metastatic colorectal cancer. World J Gastrointest Oncol 2016;8:642-655.
3. Goldberg RM, Rothenberg ML, Van Cutsem E et al. The continuum of care: a paradigm for the management of metastatic colorectal cancer. Oncologist 2007;12:38-50.
4. Ciardiello F, Tortora G. EGFR antagonists in cancer treatment. N Engl J Med 2008;358:1160-1174.
5. Lenz H-J. Anti-EGFR mechanism of action: antitumor effect and underlying cause and adverse events. Oncology 2006;20 (5 Suppl):5-13.
6. Waksal HW. Role of an anti-epidermal growth factor receptor in treating cancer. Cancer Metastasis Rev 1999;18:427-436.

7. Erbitux (Cetuximab). Full prescribing information. Princeton, NJ: Im Clone Systems Incorporated and Bristol-Myers Squibb Company, 2013.
8. European Medicines Agency. Erbitux European public assessment report, summary of product characteristics, 2014.
9. Van Cutsem E, Lenz HJ, Köhne CH et al. Fluorouracil, leucovorin, and irinotecan plus cetuximab treatment and RAS mutations in cancer. J Clin Oncol 2015;33:692-700.
10. Ciardiello F, Normanno N, Martinelli E et al. Cetuximab continuation after first progression in metastatic colorectal cancer (CAPRI-GOIM): a randomized phase II trial of FOLFOX plus cetuximab versus FOLFOX. Ann Oncol 2016;27:1055-1061.
11. Fuchs CS, Marshall J, Mitchell E et al. Randomized, controlled trial of irinotecan plus infusional, bolus, or oral fluoropyrimidines in first-line treatment of metastatic colorectal cancer: results from the BICC-C Study. J Clin Oncol 2007;25:4779-4786.
12. Giantonio BJ, Catalano PJ, Meropol NJ et al. Bevacizumab 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 2007;25:1539-1544.
13. Peeters M, Price TJ, Cervantes A et al. 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 2010;28:4706-4713.
14. Iwamoto S, Hazama S, Kato T et al. Multicenter phase II study of second-line cetuximab plus folinic acid/5-fluorouracil/irinotecan (FOLFIRI) in KRAS wild type metastatic colorectal cancer: the FLIER study. Anticancer Res 2014;34:1967-1973.
15. Mabro M, Artru P, Andre T et al. A phase II study of FOLFIRI-3 (double infusion of irinotecan combined with LV5FU) after FOLFOX in advanced colorectal cancer patients. Br J Cancer 2006;94:1287-1292.
16. Bidard FC, Tournigand C, Andre T et al. Efficacy of FOLFIRI-3 (irinotecan D1, D3 combined with LV5-FU) or other irinotecan based regimens in oxaliplatin pretreated metastatic colorectal cancer in the GERCOR OPTIMOX1 study. Ann Oncol 2009;20:1042-1047.
17. Mabro M, Louvet C, Andre T et al. Bimonthly leucovorin, infusion 5-fluorouracil, hydroxyurea, and irinotecan (FOLFIRI-2) for pretreated metastatic colorectal cancer. Am J Clin Oncol 2003;26:254-258.
18. Cohn AL, Shumaker GC, Khandelwal P et al. An open-label, single-arm, phase II trial of panitumumab plus FOLFIRI as second-line therapy in patients with metastatic colorectal cancer. Clin Colorectal Cancer 2011;10:171-177.
19. Foubert F, Matysiak-Budnik T, Touchefeu Y. Options for metastatic colorectal cancer beyond the second-line of treatment. Dig Liver Dis 2014;46:105-112.
20. Jonker DJ, O'Callaghan CJ, Karapetis CS et al. Cetuximab for the treatment of colorectal cancer. N Engl J Med 2007;357:2040-2048.
21. Van Cutsem E, Peeters M, Siena S et al. Open-label phase III trial of panitumumab plus best supportive care compared with best supportive care alone in patients with chemotherapy-refractory metastatic colorectal cancer. J Clin Oncol 2007;25:1658-1664.
22. Santini D, Vincenzi B, Addeo R et al. Cetuximab rechallenge in metastatic colorectal cancer patients: how to come away from acquired resistance? Ann Oncol 2012;23:2313-2318.
23. Jensen BV, Schou JV, Johannesen HH et al. Cetuximab every second week with irinotecan in patients with metastatic colorectal cancer refractory to 5-FU, oxaliplatin, and irinotecan: KRAS mutation status and efficacy. J Clin Oncol 2010;28:3573 (ASCO meet abstr.).
24. Pfeiffer P, Nielsen D, Yilmaz M, Iversen A, Vejlø C, Jensen BV. Cetuximab and irinotecan as third line therapy in patients with advanced colorectal cancer after failure of irinotecan, oxaliplatin and 5-fluorouracil. Acta Oncol 2007;46:697-701.
25. Pfeiffer P, Nielsen D, Bjerregaard J, Qvortrup C, Yilmaz M, Jensen B. Biweekly cetuximab and irinotecan as third-line therapy in patients with advanced colorectal cancer after failure to irinotecan, oxaliplatin and 5-fluorouracil. Ann Oncol 2008;19:1141-1145.