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Original Article

Survival benefit of metastasectomy in first-line cetuximab therapy in patients with RAS wild-type metastatic colorectal cancer: a nationwide registry

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Abstract: This multicenter study aimed to explore the survival benefit of metastasectomy by first-line cetuximab-based chemotherapy in real-world patients with *RAS* wild-type metastatic colorectal cancer (mCRC). The primary endpoints were overall survival (OS) and progression-free survival (PFS). The secondary endpoints included objective response rate (ORR), disease control rate (DCR), and metastasectomy rate. The exploratory endpoint was the optimal treatment cycle for better OS and PFS. Receiver operating characteristic curve with the area under curve (AUC) was used to identify the optimal cut-off cycle for survival outcomes. A total of 758 mCRC patients were enrolled in this study, with a median OS of 35.1 months, median PFS of 14.6 months, and metastasectomy rate of 21.4%. Left-sided mCRC had a significantly higher DCR (88.9% vs. 73.1%, $P<0.001$) and better OS (36.4 vs. 19.6 months, $P<0.001$). There were no significant differences in PFS and metastasectomy rate between left-sided and right-sided mCRC. However, mCRC patients who underwent metastasectomy over the course of treatment had better OS (54.9 vs. 28.6 months, $P<0.001$) and PFS (21.0 vs. 13.1 months, $P<0.001$) than those who did not. Notably, right-sided mCRC who benefited from first-line cetuximab-based chemotherapy to underwent metastasectomy also had favorable outcomes, on a par with left-sided mCRC. The optimal treatment cycle was 14 cycles (AUC: 0.779, $P<0.001$). Patients who received ≥14 cycles had higher metastasectomy rates (27.5% vs. 13.5%, $P<0.001$), favorable OS (42.6 vs. 23.4 months, $P<0.001$) and PFS (18.1 vs. 8.6 months, $P<0.001$), and, importantly, had comparable adverse events compared with patients who received <14 cycles of treatment. Patients who underwent

metastasectomy after or during first-line cetuximab therapy have an improved OS in both left-sided and right-sided mCRC. Furthermore, patients receive ≥14 cycles of treatment whenever possible to achieve a higher likelihood of metastasectomy was associated with favorable survival outcomes.

Keywords: *RAS* wild-type metastatic colorectal cancer, cetuximab, metastasectomy, optimal treatment cycle, overall survival, progression-free survival

Introduction

According to the GLOBOCAN report of Global Cancer Incidence and Mortality in 2020, colorectal cancer (CRC) is the second leading cause of death worldwide, with more than 1.9 million new diagnoses and an estimated 935,000 deaths in 2020 [1]. Despite advances in early detection and multimodality treatment, approximately 25% of CRC patients present with synchronous metastases at initial diagnosis, and 30-40% of logoregional CRC develop metachronous metastases after systemic treatment, with most common metastatic sites being the liver, lung, peritoneum, and lymph nodes [2-4]. The prognosis of metastatic CRC (mCRC) is extremely poor, with improvement largely dependent on primary tumor location, genetic profiles of individual tumors, response to combinations of systemic therapies, metastatic site involved, and metastasectomy [5-8]. In particular, emerging evidence highlights the critical impact of primary tumor location on CRC prognosis: right-sided CRC is associated with a poorer prognosis and lower survival rate compared to left-sided CRC [9]. The distinct disparities in survival outcomes or responses to therapeutic interventions are commonly attributed to variation in genomic and metabolomic landscapes between these two subsets of CRC [10]. Therefore, it is imperative to optimize current treatment strategies tailored to right-sided CRC, characterized by poor survival, with the overarching goal of significantly improving overall outcomes for all CRC patients.

Over the past two decades, CRC management has predominantly relied on the combination of 5-fluorouracil and folinic acid, supplemented by oxaliplatin and/or irinotecan [11, 12]. A plethora of clinical trials has subsequently delved into the exploration of targeted therapies for mCRC, unveiling a noteworthy improvement in survival outcomes when employing the doublet regimen of FOLFOX (5-fluorouracil, oxaliplatin, and folinic acid) or FOLFIRI (5-fluorouracil, irinotecan, and folinic acid) in combination with anti-epidermal growth factor receptor (EGFR) antibodies [13-15]. Therefore, anti-EGFR therapy combined with doublet or triplet chemotherapy is currently the treatment recommendations for first-line management of *RAS* wild-type mCRC, although there are some differences in treatment goals and approaches among different comprehensive guidelines [2, 3, 16-19].

The resectability of metastatic sites in mCRC is a significant factor in determining treatment options and overall prognosis. The most common metastases include portal venous spread to the liver, peritoneal spread, and lymphatic spread, as well as vascular spread to distant organs (e.g., lungs, bones, and brain). Among them, liver is a common site for metastases, and surgical resection of liver metastases, when feasible, can contribute to improved prognosis. If liver metastases are unresectable, most patients die within 1.5 years [20]. Therefore, cytoreductive strategies are crucial for the management of mCRC, providing various potential advantages, such as decreasing tumor burden, enhancing response to systemic therapy, and improving the feasibility of surgical resection of these metastases. Therefore, cytoreductive strategies are recommended as treatment goal in the European Society for Medical Oncology (ESMO) and American Society of Clinical Oncology (ASCO) guidelines, which contribute to long-term survival outcomes in patients with colorectal metastases to liver, lung, peritoneum, and lymph node [20-23]. In several clinical trials of mCRC patients treated with first-line cetuximab plus chemotherapy, early tumor shrinkage during treatment was considered a favorable prognostic factor and was significantly associated with better survival outcomes and health-related quality of life [24-26]. Moreover, mCRC patients who achieve sufficient tumor shrinkage are more likely to undergo metastasectomy, which has been shown to improve survival [27, 28].

While first-line cetuximab-based chemotherapy shows potential for increasing the likelihood of metastasectomy, the extent of its effectiveness in this regard, particularly in terms of the

associated survival outcomes post-metastasectomy, remains uncertain. Furthermore, it is currently unclear what the optimal treatment cycle is to achieve higher metastasectomy rates, better treatment response, and favorable survival outcomes without significantly increasing adverse events. Given that most current studies are confounded by small sample sizes and population heterogeneity, this multicenter registry study was conducted to explore the impact of first-line cetuximab-based chemotherapy in metastasectomy rate and survival benefit in real-world *RAS* wild-type mCRC patients by registry study.

Methods

Study design and population

Patients with mCRC who received cetuximab-based chemotherapy as first-line treatment between November 2016 and December 2020 were enrolled in this study. The inclusion criteria were 1) 18 years of age or older; 2) histologically confirmed RAS wild-type metastatic colorectal tumors (exons 2, 3, and 4 of both *KRAS* and *NRAS*); and 3) had received more than 3 cycles of first-line cetuximab-based chemotherapy. Patients who did not meet the inclusion criteria or were unwilling to participate were excluded. This retrospective, multicenter observational study was conducted was conducted in accordance with the Declaration of Helsinki, and the study protocol and all amendments were approved by the institutional review board (IRB) or ethics committees of all the 14 participating institutions. The institution of the ethic committee and the corresponding approved IRB numbers were as follows: 1) Taipei Veterans General Hospital (approved number: 2017-12-003A); 2) National Taiwan University Hospital (approved number: 202108081RINA); 3) Shuang Ho Hospital (approved number: N202110007); 4) Linkou Chang Gung Memorial Hospital (approved number: 202101933B0); 5) China Medical University Hospital (approved number: CMUH111-REC3-054); 6) Taichung Veterans General Hospital (approved number: CE21536B); 7) Changhua Christian Hospital (approved number: 211001); 8) National Taiwan University Hospital Yunlin Branch (approved number: 202107123RIPB); 9) Chiayi Chang Gung Memorial Hospital (approved number: 2021019-33B0); 10) National Cheng Kung University Hospital (approved number: A-ER-110-471); 11) Kaohsiung Medical University (approved number: KMUHIRB-E(I)-20210246); 12) Kaohsiung Chang Gung Memorial Hospital (approved number: 202101933B0); 13) Kaohsiung Veterans General Hospital (approved number: KSVGH21-CT14-06); and 14) E-DA Hospital (approved number: EMRP-110-167). Due to the retrospective nature of this study and the use of anonymized clinical data for all analyses, written informed consent was waived by the institutional review boards of all hospitals/medical centers.

Outcomes and assessments

The primary endpoints were overall survival (OS) and progression-free survival (PFS). The period of OS was calculated as the interval between the date of receiving first-line cetuximab-based chemotherapy and the date of the last follow-up or death, whichever occurred first. PFS was defined as the duration between the date of first administration of first-line cetuximab-based chemotherapy and the date of tumor progression or death from any cause. The secondary endpoints included objective response rate (ORR), disease control rate (DCR), duration of treatment (DOT), and metastasectomy rate. The best confirmed treatment response was assessed by independent central review according to the Response Evaluation Criteria in Solid Tumors (RECIST, Version 1.1). The best confirmed treatment response is the record from treatment initiation to disease progression, classified as complete response (CR), partial response (PR), stable disease (SD), and disease progression (SD). ORR was defined as the proportion of mCRC patients who achieved a CR or PR among the evaluators, while DCR was defined as the proportion of patients who achieved a CR or PR or SD. DOT was defined as the interval between the date of a patient received first-line cetuximab-based chemotherapy and the date of the last treatment. The exploratory endpoint was the optimal treatment cycle of first-line cetuximab plus chemotherapy to obtain a better OS and PFS. Adverse events (AEs) were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) [29], and the incidence of AEs were calculated and further classified into

Table 1. Demographics and clinical characteristics of patients with *RAS* wild-type mCRC (N=758)

Characteristics	N	%
Gender		
Male	514	67.8%
Female	244	32.2%
Age, years (Median with IQR)	61.82 (52.12, 70.49)	
ECOG		
0	500	66.0%
1	224	29.6%
2	20	2.6%
≥3	13	1.7%
Unknown	1	0.1%
Location of primary tumor		
Left-sided	681	89.8%
Right-sided	72	9.5%
Both-sided	3	0.4%
Unknown	2	0.3%
Metachronous or synchronous metastasis		
Metachronous	286	37.7%
Synchronous	468	61.7%
Unknown	4	0.5%
Metastases sites‡		
Liver	466	61.6%
Lung	198	26.2%
Peritoneum	157	20.7%
Lymph nodes	115	15.2%
Others	147	19.4%
Unknown	4	0.5%
BRAF Status		
Wild-Type	547	72.2%
V600E mutation	21	2.8%
Unknown	190	25.1%
MMR Status		
pMMR	364	48.0%
dMMR	30	4.0%
Unknown	364	48.0%

Abbreviations: ECOG, Eastern Cooperative Oncology Group; dMMR, deficient mismatch repair; pMMR, proficient mismatch repair. ‡More than one metastatic site could be present in the same patient. A total of 752 patients had records of resection of metastatic sites.

hematological adverse events and non-hematological adverse events.

Statistical analyses

Continuous data are summarized as the mean ± standard deviation (SD) or median with interquartile range. Categorical data are presented as frequency and percentage. Categorical data were compared using Chi-square test or Fisher's exact test according to the data distribution, while continuous data were compared using the Mann-Whitney U test. OS and PFS were evaluated by Kaplan-Meier survival analysis, and the log-rank test was used to compare time-to-event distributions. The scores of treatment cycles for first-line cetuximab-based chemotherapy was evaluated using the Receiver Operating Characteristic (ROC) curve and the area under the ROC curve (AUC). The optimal cut-off value was determined by calculating the Youden index for maximizing sensitivity and specificity. All statistical analyses performed in this study were using the Statistical Package for the Social Sciences (version 20, International Business Machines Corporation, Armonk, NY, USA). A two-tailed *P*-value less than 0.05 was considered statistically significant.

Results

Patient characteristics

Table 1 shows the demographic and clinical characteristics of patients with *RAS* wild-type mCRC. A total of 758 patients with *RAS* wild-type mCRC who received first-line cetuximab-based chemotherapy were included in the study cohort, with a mean age of 61.60 ± 13.05 years (median: 61.8 years; interquartile range, 52.1-70.5 years). Most patients were male (67.8%) and had an ECOG score 0 or 1 (95.6%). Most metastases were synchronous (61.7%) and located at left side colon (89.8%). The most common sites of metastases were liver (61.6%), lung (26.2%), peritoneum (20.7%), and lymph nodes (15.2%). Most mCRC were proficient mismatch repair (pMMR) and wild-type *BRAF* tumors.

Treatment response and survival outcomes

In this study cohort, the best confirmed responses to first-line cetuximab-based chemo-

Table 2. Treatment response and survival outcome to first-line cetuximab-based chemotherapy in patients with *RAS* wild-type mCRC

	Total (N=758)		Left-sided (N=681)†		Right-sided (N=72)		*p*-value
Treatment Response							0.002
CR	71	9.9%	62	9.6%	8	11.9%	0.573
PR	367	50.9%	338	52.1%	26	38.8%	0.030
SD	193	26.8%	177	27.3%	15	22.4%	0.343
PD	90	12.5%	72	11.1%	18	26.9%	<0.001
ORR							0.082
CR+PR	437	60.7%	400	61.6%	34	50.7%	
SD+PD	282	39.1%	249	38.4%	33	49.3%	
DCR							<0.001
CR+PR+SD	630	87.5%	577	88.9%	49	73.1%	
PD	90	12.5%	72	11.1%	18	26.9%	
Not evaluable/Unknown	29	-%	25	-%	4	-%	
Survival Outcome, median (95% CI)							
OS	35.1 (32.3-38.0)		36.4 (33.4-39.4)		19.6 (10.2-29.1)		<0.001
PFS	14.6 (13.6-15.6)		14.9 (13.8-15.9)		11.7 (8.7-14.7)		0.217
Metastasectomy rate (95% CI)	21.4% (18.5-24.5)		22.0% (18.9-25.3)		16.9% (9.0-27.7)		0.324
Metastatic site resection‡							0.609
R0	130	17.2%	120	17.6%	9	12.5%	
R1/R2	33	4.4%	30	4.4%	3	4.2%	
No Resection	589	77.7%	526	77.2%	59	81.9%	

Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progression disease; ORR, objective response rate; DCR, disease control rate; CI, confidence interval. †There were 3 patients with primary tumors located on the left and right side of the colon with unknown origin, while 2 patients had missing data. ‡More than one metastatic site could be present in the same patient. A total of 160 patients had records of resection of metastatic sites. Data were missing for 9 patients.

therapy were CR (9.9%), PR (50.9%), SD (26.8%), and PD (12.5%), with an ORR of 60.7% and a DCR of 87.5% (**Table 2**). The median OS of total population was 35.1 months (95% CI: 32.3-38.0 months; **Figure 1A**), and the median PFS was 14.6 months (95% CI: 13.6-15.6 months; **Figure 1B**). The overall metastasectomy rate was 21.4% (95% CI: 18.45-24.5 months), and 130 of 163 (79.8%) were R0 resections.

In the subgroup analysis stratified by metastatic location, there was a significant difference in treatment response between the left-sided and right-sided mCRC subgroups (P=0.002). Left-sided mCRC had a significantly higher PR rate (52.1% vs. 38.8%, P=0.030) and DCR (88.9% vs. 73.1%, P<0.001) than right-sided mCRC. However, there were no significant differences between the left-sided and right-sided subgroups in terms of CR and ORR rates (both P>0.05). The Kaplan-Meier survival analyses showed that patients with left-sided mCRC had a better OS than patients with right-sided mCRC (**Figure 1C**; 36.4 vs. 19.6 months, P<0.001). No significant difference in PFS was found between the two subgroups (**Figure 1D**; 14.9 vs. 11.7 months, P=0.217). In addition, metastasectomy rate did not differ significantly between the two subgroups over the course of treatment (22.0% vs. 16.9%, P=0.324). Nonetheless, mCRC patients who underwent metastasectomy over the course of first-line cetuximab-based chemotherapy had better OS (**Figure 1E**) and PFS (**Figure 1F**) than those who did not undergo metastasectomy (P<0.001). The 1-, 3-, and 5-year OS of mCRC patients who underwent metastasectomy were 99.4%, 78.9%, and 36.3%, respectively, whereas the 1-, 3-, and 5-year OS for mCRC patients who did not undergo metastasectomy were 80.5%, 37.5%, and 23.0%, respectively.

The outcomes of mCRC patients who underwent metastasectomy

Given the above finding that metastasectomy is beneficial on survival outcomes, subgroup

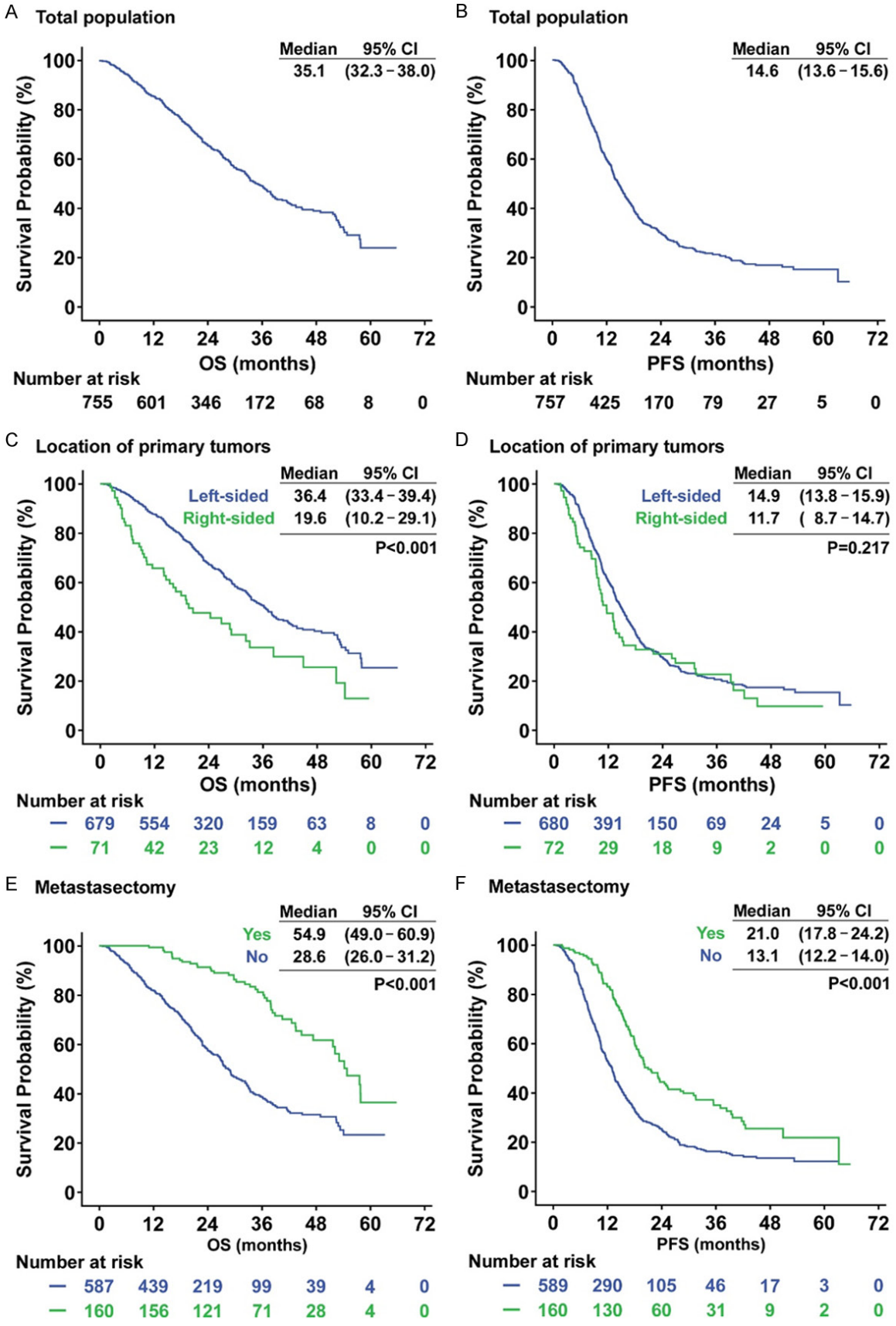
A
Total population
Median 95% CI
35.1 (32.3 – 38.0)
Survival Probability (%)
OS (months)
Number at risk
755 601 346 172 68 8 0
B
Total population
Median 95% CI
14.6 (13.6 – 15.6)
Survival Probability (%)
PFS (months)
Number at risk
757 425 170 79 27 5 0
C
Location of primary tumors
Median 95% CI
Left-sided 36.4 (33.4 – 39.4)
Right-sided 19.6 (10.2 – 29.1)
P<0.001
Survival Probability (%)
OS (months)
Number at risk
679 554 320 159 63 8 0
71 42 23 12 4 0 0
D
Location of primary tumors
Median 95% CI
Left-sided 14.9 (13.8 – 15.9)
Right-sided 11.7 (8.7 – 14.7)
P=0.217
Survival Probability (%)
PFS (months)
Number at risk
680 391 150 69 24 5 0
72 29 18 9 2 0 0
E
Metastasectomy
Median 95% CI
Yes 54.9 (49.0 – 60.9)
No 28.6 (26.0 – 31.2)
P<0.001
Survival Probability (%)
OS (months)
Number at risk
587 439 219 99 39 4 0
160 156 121 71 28 4 0
F
Metastasectomy
Median 95% CI
Yes 21.0 (17.8 – 24.2)
No 13.1 (12.2 – 14.0)
P<0.001
Survival Probability (%)
PFS (months)
Number at risk
589 290 105 46 17 3 0
160 130 60 31 9 2 0

Figure 1. Survival outcomes of patients with *RAS* wild-type mCRC. Kaplan-Meier survival plots of OS (A) and PFS (B) for total population (N=758). Kaplan-Meier survival plots of OS (C) and PFS (D) accrdoing to the right- and left-sided mCRC. Kaplan-Meier survival plots of OS (E) and PFS (F) accrdoing to metastasectomy. The Log-Rank test was used to assess the survival difference between groups. A *p*-value less than 0.05 was considered statistically significant.

analysis stratified by metastasectomy was further assessed in left-sided and right mCRC. For left-sided mCRC, patients who received metastasectomy over the course of treatment had significantly better OS (54.9 vs. 29.2 months, *P*<0.001; **Figure 2A**) and PFS (20.1 vs. 13.1 months, *P*<0.001; **Figure 2B**) than those who did not undergo metastasectomy. Likewise, OS (52.3 vs. 16.7 months, *P*=0.003; **Figure 2C**) and PFS (39.7 vs. 10.3 months, *P*=0.001; **Figure 2D**) were significantly longer in patients with right-sided mCRC who underwent metastasectomy due to the benefit of first-line cetuximab therapy. Although cetuximab treatment showed favorable survival benefits for left-sided mCRC, there were no significant differences in OS (54.9 vs. 52.3 months, *P*=0.779; **Figure 2E**) and PFS (20.1 vs. 39.7, *P*=0.118; **Figure 2F**) between patients with left-sided and right-sided mCRC who underwent metastasectomy over the course of first-line cetuximab therapy.

Next, the survival outcomes of curative-intent surgical resection of different metastatic sites were assessed. **Table 3** shows the OS and PFS of mCRC patients who had resected liver or lung or peritoneum or others colorectal metastases. Most metastases were resected to achieve curative R0 status. There were significant differences in OS and PFS between mCRC patients who underwent metastasectomy in the liver, lung, peritoneal, or other site during first-line cetuximab-based chemotherapy (*P*< 0.05, **Table 3**). However, there were no significant differences in OS and PFS among mCRC patients who underwent liver metastasectomy, lung metastasectomy, and peritoneal metastasectomy (*P*>0.05, **Table 3**). The finding suggests that mCRC patients who benefited from first-line cetuximab treatment and underwent metastasectomy had comparable survival benefit regardless of liver, lung or peritoneal metastases. Regarding the DOT, there were no significant difference in DOT between patients received metastasectomy for liver, lung, peritoneal, or other metastases (14.3, 22.3, 14.0, and 12.3 months, respectively; *P*=0.231).

Optimal number of cycles of the first-line cetuximab-based chemotherapy

ROC curve analysis was further explored to explore the optimal cycle of the first-line cetuximab-based chemotherapy for mCRC patients. As shown in **Figure 3A**, the optimal number of cycles for first-line cetuximab-based chemotherapy was 14 cycles, with an AUC of 0.779, a sensitivity of 71.8%, and a specificity of 75.1% (*P*<0.001). Patients with mCRC who received ≥14 cycles of first-line cetuximab-based chemotherapy had significantly longer OS (42.6 vs. 23.4 months, *P*<0.001; **Figure 3B**) and PFS (18.1 vs. 8.6 months, *P*<0.001; **Figure 3C**) than those who received <14 cycles. The 1-, 3-, and 5-year OS for mCRC patients who received ≥14 treatment cycles were 97.8%, 59.3%, and 34.8%, respectively. While the 1-, 3-, and 5-year OS for mCRC patients who received <14 treatment cycles were 67.8%, 32.5%, and 11.4%, respectively. Furthermore, patients who received ≥14 cycles of treatment had significantly higher metastasectomy rate (27.5% vs. 13.5%, *P*<0.001), ORR (80.3% vs. 35.9%, *P*<0.001), and DCR (98.5% vs. 74.1%, *P*<0.001) than those who received <14 cycles (Supplementary Table 2). There was no significant difference in AEs in mCRC patients stratified by the optimal 14 treatment cycles (Supplementary Table 3).

Safety

The frequency and type of hematological and non-hematological AEs in our study cohort were shown in Supplementary Table 1. The most common hematologic AEs were anemia (39.5%) and neutropenia (32.2%), and the most common non-hematologic adverse events were skin reaction (63.0%), fatigue (44.5%), and nausea (37.6%). Most of these AEs were grade 1 and 2.

Discussion

This study aimed to assess the real-world evidence related to first-line cetuximab-based chemotherapy in mCRC patients with *RAS* wild-type status and explore the optimal treatment cycles and the survival benefit of metastasec-

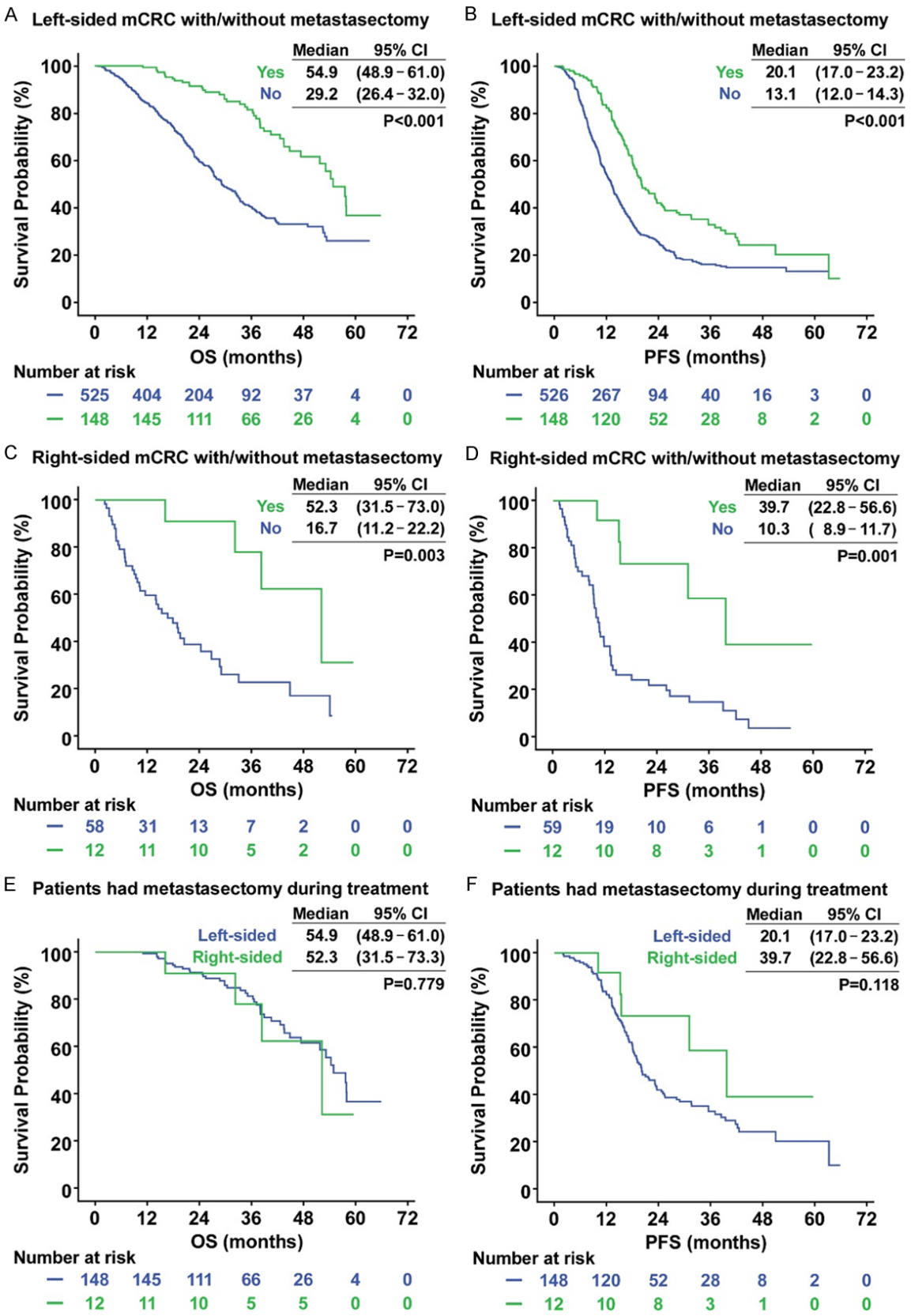

Figure 2. Subgroup analysis of survival outcomes of patients with RAS wild-type mCRC based on metastasectomy across overall population. Kaplan-Meier survival plots of OS (A) and PFS (B) for patients with left-sided mCRC ac-

cording to whether they underwent metastasectomy. Kaplan-Meier survival plots of OS (C) and PFS (D) for patients with right-sided mCRC according to whether they underwent metastasectomy. Kaplan-Meier survival plots of OS (E) and PFS (F) stratified by lef-sided and right-sided mCRC in patients who underwent metastasectomy during first-line cetuximab-based chemotherapy. The Log-Rank test was used to assess the survival difference between groups. A *p*-value less than 0.05 was considered to be statistically significant.

Table 3. Survival outcomes, duration of treatment, and resection status stratified by metastatic site resection

	Liver (N=113)		Lung (N=23)		Peritoneum (N=15)		Others† (N=15)		*p*-value
Survival outcomes, months, 95% CI									
OS	54.3	47.44-57.89	Not reached	N/A	58.0	N/A	35.1	26.10-44.15	0.004
PFS	21.0	18.17-25.30	39.4	20.07-42.55	19.9	10.81-42.18	12.7	9.12-16.24	0.003
DOT, median with IQR	14.3	9.03, 21.29	22.3	10.94, 31.05	14.0	8.18, 22.74	12.3	8.67, 18.33	0.231
Metastasectomy, N%									0.105
R0	92	81.42%	17	73.9%	7	46.67%	13	86.7%	
R1/R2	19	16.81%	6	26.1%	6	40.00%	2	13.3%	
Unknown	2	1.77%	0	0.00%	2	13.33%	0	0.00%	

Abbreviations: OS, overall survival; PFS, progression-free survival; DOT, duration of treatment. †Others included ovary, distant lymph-node, common iliac nodal, uterus, and bladder. More than one metastatic site could be present in the same patient. A total of 160 patients had records of resection of metastatic sites.

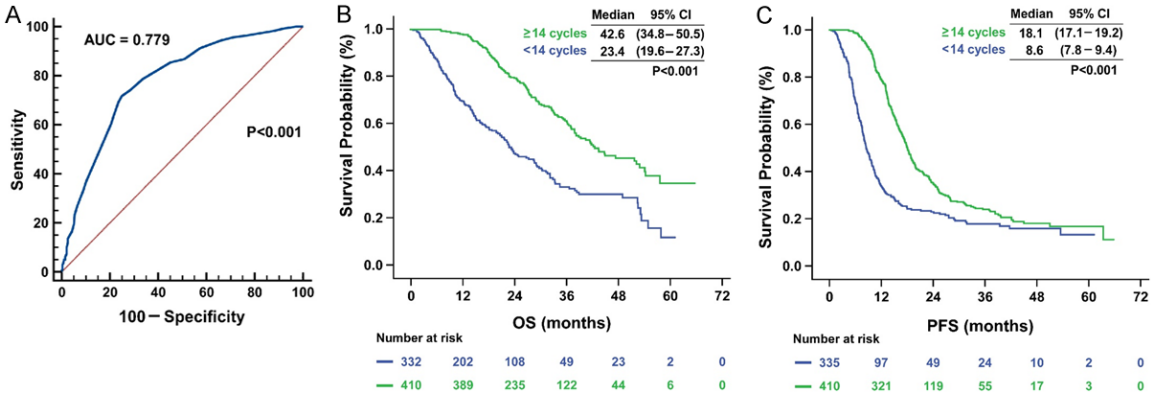

Figure 3. First-line cetuximab-based chemotherapy ≥14 cycles associated with better survival outcomes in mCRC. A. The ROC curve analysis of optimal cut-off value of treatment cycle. The optimal cycle of first-line cetuximab-based chemotherapy was 14 cycles, with an AUC of 0.779 (P<0.001; Sensitivity =71.8%, Specificity =75.1%). B. Kaplan-Meier survival plot of OS according to optimal cycle of first-line cetuximab-based chemotherapy. C. Kaplan-Meier survival plot of PFS according to optimal cycle of first-line cetuximab-based chemotherapy. The Log-Rank test was used to assess the survival difference between groups. A *p*-value less than 0.05 was considered to be statistically significant.

tomy. The results of this study revealed that treatment for ≥14 cycles brought benefits of higher metastasectomy rates and better treatment response, leading to favorable survival outcomes without significantly increased AEs. For peritoneal metastases with poorer prognosis, these patients who benefited from treatment and underwent peritoneal metastasectomy had comparable survival outcomes to patients who underwent liver or lung metastasectomy, of which it was consistent with results from Li *et al*. [21]. Even for right-sided mCRC with an expected poor prognosis to standard chemotherapy, first-line cetuximab-based chemotherapy with metastasectomy put it on a par with left-sided mCRC. Therefore, this study recommends that patients with mCRC should receive more than 14 cycles of first-line cetuximab-based chemotherapy and metastasectomy whenever possible, as it can lead to higher response rates and favorable oncological outcomes.

In this real-world evidence, the observed survival benefit of first-line cetuximab-based chemotherapy in Taiwanese patients with mCRC

also supported by the FIRE-3 trial and the CELIM study. The OS and PFS of mCRC patients who received FOLFIRI plus cetuximab in the FIRE-3 trial were 33.1 and 10.3 months, respectively [30], which were comparable to our real-world findings in 758 Taiwanese patients with mCRC (OS: 35.1 months; PFS: 14.6 months). In addition, survival outcomes stratified by left-sided and right-sided mCRC were also similar to the results in this study. Another analysis FIRE-3 trial by Modest *et al*. also demonstrated that resection of metastases was associated with improved post-best response survival, and importantly, this effect was thought to be predominantly from the cetuximab therapy [31]. Similar results were also observed in the CELIM study [32], which showed that favorable OS was observed in patients benefiting from cetuximab plus FOLFOX/FOLFIRI regimens followed by resection of their colorectal liver metastases. In a recent study comparing the LICC, CELIM, and FIRE-3 prospective randomized trials [33], the median OS in mCRC patients with liver-limited disease after secondary hepatic resection was 66.1 months in LICC, 53.9 months in CELIM, and 56.2 months in FIRE-3-LLD. This survival outcome was also similar to our findings in mCRC patients who underwent liver metastasectomy after cetuximab therapy (54.3 months). With regard to peritoneal metastases, mCRC patients with peritoneal metastases are generally considered to be associated with a poorer prognosis. Consistently, mCRC patients with peritoneal metastases only in our study cohort had the lowest OS. The median OS were 26.9 months, 39.0 months, and not reached for mCRC patients with peritoneal, liver, and lung metastases, respectively (P=0.002). Notably, despite the poorer prognosis of peritoneal metastases, mCRC patients with peritoneal metastases who underwent metastasectomy due to benefit from first-line cetuximab chemotherapy did have improved survival outcomes, on a par with mCRC patients with liver metastases (median OS: 58.0 vs. 54.3, P>0.05; median PFS: 19.9 vs. 21.0, P>0.05). Therefore, our results suggest that metastasectomy should be performed in mCRC patients over the course of first-line cetuximab-based chemotherapy, also true for poor prognostic peritoneal metastases. Even for right-sided mCRC with an expected poor prognosis to standard chemotherapy, first-line cetuximab-based chemotherapy with metastasectomy put it on a par with left-sided mCRC.

First-line cetuximab-based chemotherapy showed promising efficacy in increasing metastasectomy rate to reduce the burden of tumors, and thereby improving the survival outcomes. Nonetheless, it remains unclear how many cycles of first-line cetuximab chemotherapy are needed to achieve the maximum survival benefit. In clinical practice, more treatment cycles may lead to more chemotherapy-related toxicities, resulting in increased complication rates and severity of adverse events [34-36]. Likewise, a recent study also indicated that the oncological outcomes in the ≥7-cycle group were significantly better than those in the 6-cycle group among patients with mCRC undergoing Metastasectomy [36]. Although it is unclear whether this difference is attributable to the addition of cetuximab, it is noteworthy that ≥14 cycles doubled the complete metastasectomy (R0) and response rates but did not increase the incidence of AEs. Therefore, we recommended that patients with mCRC would benefit receive more than 14 cycles of first-line cetuximab-based chemotherapy and metastasectomy whenever possible, as it can lead to higher response rates and favorable oncological outcomes, although patients may experience a variety of physical and psychological symptoms that affect their quality of life.

Although this study revealed the optimal treatment cycles of first-line cetuximab-based chemotherapy in a real-world mCRC population, heterogenicity in regimens combined with cetuximab may be highly susceptible to bias. To address this bias, we further analyzed regimens combined with cetuximab and found that the majority of regimens were FOLFIRI (82.5%), followed by FOLFOX (13.5%). Therefore, subgroup analyses according the FOLFIRI and FOLFOX regimens were further conducted. The results of ROC analysis for patients who received cetuximab plus FOXFOX regimen were the same as for the total population, with an optimal treatment cycle of 14 (P<0.001). Moreover, the optimal treatment cycle of cetuximab plus FOLFIRI was 12 cycles (P<0.001).

This study has some limitations. First, although this study has the strength of a large study cohort, it is still limited by its retrospective nature and cannot completely eliminate selec-

tion bias due to the complex combination regimens and subsequent second- or third-line treatment. Second, the timing of metastasectomy is not been set based on established policies, but depends on oncologic considerations and general health status, as well as the patient's willingness. Therefore, potential bias cannot be ruled out. Moreover, records of the timing of metastasectomy over the course of treatment were unavailable. Therefore, the time interval between initiation of treatment and metastasectomy could not be calculated, nor the correlation between treatment duration and metastasectomy. Third, the *BRAF* and MMR status of many mCRC patients was unknown due to lack of routine testing in hospitals. Limited by the inherently low proportion, further subgroup analysis of those with BRAF mutation and/or MMR deficiency could not be performed. Future prospective studies with large sample size are warranted to validate the results of this study and overcome these limitations.

Conclusion

This multicenter retrospective study with a large mCRC population not only confirmed the clinical benefit of cetuximab-based chemotherapy in the first-line treatment of patients with *RAS* wild-type mCRC, but also revealed the optimal treatment cycles to achieve higher metastasectomy rates and longer survival outcomes. Giving more than 14 cycles of cetuximab-based first-line chemotherapy is recommended, because higher cycles of treatment did not increase prominent toxicity but improved the likelihood of metastasectomy, which was found to be associated with higher response rates and favorable OS and PFS. Even for peritoneal metastases with very poor prognosis, peritoneal metastasectomy can achieve comparable survival outcomes to lung or liver metastasectomy. Furthermore, first-line cetuximab-based chemotherapy is effective for right-sided mCRC with metastasectomy, and the outcomes are on a par with left-sided mCRC with metastasectomy.

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Disclosure of conflict of interest

None.

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Supplementary Table 1. Summary of all adverse events at first-line cetuximab-based chemotherapy in patients with *RAS* wild-type mCRC (N=758)

	All grade (N, %)		Grade 1/2 (N, %)		Grade 3/4 (N, %)	
Hematologic						
Anemia	299	39.5%	287	37.9%	13	1.7%
Neutropenia	244	32.2%	199	26.3%	46	6.1%
Febrile neutropenia	12	1.6%	7	0.9%	5	0.7%
Thrombocytopenia	48	6.3%	45	5.9%	3	0.4%
non-Hematologic						
Skin reaction	477	63.0%	455	60.0%	23	3.0%
Paronychia	163	21.5%	164	21.6%	0	0.0%
Abdominal pain	59	7.8%	56	7.4%	3	0.4%
Diarrhea	189	25.0%	180	23.7%	10	1.3%
Nausea	285	37.6%	281	37.1%	5	0.7%
Vomiting	214	28.3%	206	27.2%	9	1.2%
Fatigue	337	44.5%	326	43.0%	12	1.6%
Infusion reaction	13	1.7%	12	1.6%	0	0.0%
Infection	22	2.9%	18	2.4%	4	0.5%
ALT increased	78	10.3%	76	10.0%	2	0.3%
AST increased	82	10.8%	80	10.6%	2	0.3%
Bilirubin increased	26	3.4%	24	3.2%	2	0.3%
Creatinine Increased	44	5.8%	40	5.3%	4	0.5%
Hypomagnesemia	17	2.2%	17	2.2%	0	0.0%

Abbreviations: ALT, alanin aminotransferase; AST, aspartat aminotransferase.

Supplementary Table 2. Survival outcomes, resection status, and treatment response in patients with RAS wild-type mCRC stratified according the optimal cycle of treatment

	<14 cycles (N=335)		≥14 cycles (N=410)		*P*-value
Outcomes, median month, 95% CI					
OS	23.4	19.6-27.3	42.6	34.8-50.5	<0.001
PFS	8.6	7.8-9.4	18.1	17.1-19.2	<0.001
Metastasectomy rate, N %	45	13.5%	111	27.5%	<0.001
R0	35	76.5%	89	83.2%	
R1/R2	9	23.5%	20	16.8%	
No Resection	289	-%	292	-%	
Unknown	1	-%	2	-%	
Treatment Response, N %					<0.001
CR	15	4.9%	53	13.3%	<0.001
PR	96	31.1%	268	67.0%	<0.001
SD	118	38.2%	73	18.3%	<0.001
PD	80	25.9%	6	1.5%	<0.001
ORR	111	35.9%	321	80.3%	<0.001
DCR	229	74.1%	394	98.5%	<0.001
Not evaluable/Unknown	26	-%	10	-%	

Supplementary Table 3. Adverse Events in patients with *RAS* wild-type mCRC stratified according the optimal cycle of treatment

	All grade				*p*-value	Grade 1/2				*p*-value	Grade 3/4				*p*-value
	<14 cycles		≥14 cycles			<14 cycles		≥14 cycles			<14 cycles		≥14 cycles		
Hematologic															
Anemia	156	46.6%	140	34.1%	0.001	148	44.2%	136	33.2%	0.002	8	2.4%	4	1.0%	0.151
Neutropenia	96	28.7%	144	35.1%	0.060	74	22.1%	121	29.5%	0.022	22	6.6%	23	5.6%	0.644
Febrile neutropenia	8	2.4%	4	1.0%	0.151	4	1.2%	3	0.7%	0.517	4	1.2%	1	0.2%	0.180
Thrombocytopenia	29	8.7%	19	4.6%	0.026	27	8.1%	18	4.4%	0.036	2	0.6%	1	0.2%	0.591
Non-Hematologic															
Skin reaction	182	54.3%	287	70.0%	<0.001	170	50.7%	276	67.3%	<0.001	12	3.6%	11	2.7%	0.480
Paronychia	60	17.9%	101	24.6%	0.027	60	17.9%	101	24.6%	0.027	0	0.0%	0	0.0%	-
Abdominal pain	36	10.7%	22	5.4%	0.007	34	10.1%	21	5.1%	0.009	2	0.6%	1	0.2%	0.591
Diarrhea	89	26.6%	98	23.9%	0.404	83	24.8%	94	22.9%	0.555	6	1.8%	4	1.0%	0.358
Nausea	128	38.2%	154	37.6%	0.856	125	37.3%	152	37.1%	0.946	3	0.9%	2	0.5%	0.662
Vomiting	92	27.5%	120	29.3%	0.573	85	25.4%	118	28.8%	0.289	7	2.1%	2	0.5%	0.086
Fatigue	158	47.2%	175	42.7%	0.221	149	44.5%	172	42.0%	0.488	9	2.7%	3	0.7%	0.042
Infusion reaction	6	1.8%	7	1.7%	0.930	6	1.8%	7	1.7%	0.930	0	0.0%	0	0.0%	-
Infection	16	4.8%	5	1.2%	0.004	13	3.9%	4	1.0%	0.008	3	0.9%	1	0.2%	0.332
ALT increased	35	10.4%	40	9.8%	0.755	35	10.4%	38	9.3%	0.590	0	0.0%	2	0.5%	0.504
AST increased	40	11.9%	41	10.0%	0.397	40	11.9%	39	9.5%	0.284	0	0.0%	2	0.5%	0.504
Bilirubin increased	16	4.8%	9	2.2%	0.052	14	4.2%	9	2.2%	0.121	2	0.6%	0	0.0%	0.202
Creatinine Increased	24	7.2%	18	4.4%	0.102	23	6.9%	15	3.7%	0.048	1	0.3%	3	0.7%	0.632
Hypomagnesemia	13	3.9%	4	1.0%	0.011	13	3.9%	4	1.0%	0.007	0	0.0%	0	0.0%	-

Abbreviations: ALT, alanin aminotransferase; AST, aspartat aminotransferase.