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ORIGINAL ARTICLE **CME**

Treatment Outcomes in Patients Receiving Regorafenib for Metastatic Colon Cancer

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ABSTRACT

Objectives: *To review the treatment outcomes of patients with chemorefractory metastatic colorectal cancer receiving the multikinase inhibitor regorafenib.*

Methods: *This was a retrospective cohort study including patients who received regorafenib after failure of standard irinotecan- and oxaliplatin-based chemotherapy with or without biologics from 2016 to 2018 in a single centre in Hong Kong.*

Results: *Fourteen patients met the inclusion criteria. All had good general condition (i.e., Eastern Cooperative Oncology Group score 1). Seven patients had received bevacizumab previously. Median progression-free survival (PFS) was 12.4 weeks and median overall survival (OS) was 26.5 weeks. Eight patients had grade ≥3 adverse events and 10 (71.4%) required temporary treatment suspension. The commonest grade ≥3 adverse events were palmar-plantar erythrodysaesthesia and fatigue (both 28.6%). Patients with a carcinoembryonic antigen drop of ≥50% from baseline enjoyed longer PFS, though not to a significant extent. OS was longer for left-sided primary tumours (202 vs. 57 days, p = 0.001). Two patients with good performance after progression received trifluridine-tipiracil. Their median OS was 400 days.*

Conclusion: *Our experience with regorafenib monotherapy for patients with chemorefractory metastatic colorectal cancer was comparable to the landmark trials. The grade ≥3 adverse events were frequent, and dose reduction or treatment delay was required. Potentially favourable prognostic factors included a left-sided primary tumour and a carcinoembryonic antigen drop from baseline. Those who received further treatment after regorafenib enjoyed reasonably long survival. Treatment after regorafenib with newer strategies should be considered in those who remain functional.*

Key Words: *Colorectal neoplasms; Protein kinase inhibitors*

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Ethics Approval: This study was approved by the Research Ethics Committee (Kowloon Central/Kowloon East) of the Hospital Authority, Hong Kong (Ref KC/KE-19-0046-ER/4). The requirement for patient consent was waived. All patients were treated in compliance with the Declaration of Helsinki.

中文摘要

瑞戈非尼對大腸癌轉移患者的治療結果

霍善智、張嘉文、郭婉琳、黃錦洪

目的：探討多激酶抑制劑瑞戈非尼對化療難治性大腸癌轉移患者的治療結果。

方法：這項回顧性隊列研究納入2016年至2018年於香港單一中心進行標準伊立替康和奧沙利鉑化療無效後接受瑞戈非尼治療合用或未合用生物製劑的患者。

結果：14名患者符合納入標準。所有患者的身體狀況較好（ECOG 1分），當中7名患者曾接受貝伐單抗治療。無惡化存活期中位數為12.4週，總體存活期中位數為26.5週。8名患者出現≥3級不良事件，10名患者（71.4%）須暫停治療。最常見≥3級不良事件包括掌足紅腫綜合徵和疲勞（均為28.6%）。癌胚抗原從基線下降≥50%的患者有更長無惡化存活期，但只有邊緣顯著性。左側原發腫瘤患者的總體存活期較長（202天比57天，p = 0.001）。兩名患者在瑞戈非尼治療失敗後因體能狀態較佳，遂以三氟胸苷—替吡嘧啶作進一步治療。他們的總體存活期中位數為400天。

結論：本研究的瑞戈非尼單藥治療化療難治性大腸癌轉移患者的經驗與具有里程碑意義的試驗相若。≥3級不良事件很常見，須減少劑量或延遲治療。潛在的有利預後因素包括左側原發腫瘤和癌胚抗原從基線下降。瑞戈非尼後接受進一步治療患者有較長存活期。使用瑞戈非尼後仍保持功能的患者，可考慮以新策略作進一步治療。

INTRODUCTION

Colorectal cancer is the commonest malignancy in Hong Kong, with an age-standardised incidence rate of 35.7 per 100 000 population in 2016.[1] Up to 23% of patients have metastatic disease on presentation, and the 5-year overall survival (OS) is 14%.[2]

Traditionally, chemotherapy and biologics using fluoropyrimidine, irinotecan and oxaliplatin, with or without anti–vascular endothelial growth factor (VEGF) agents and anti–epithelial growth factor receptor (EGFR) agents for *RAS* wild-type tumours, were the main treatment strategies for inoperable or metastatic colorectal cancer (mCRC). Despite the range of available combination therapies, OS remained in the range of 20 to 30 months.[3] Options beyond these standard treatments were limited, with regorafenib and trifluridine-tipiracil being the only two Food and Drug Administration (FDA)–approved treatments for this group of patients.[4]

Regorafenib is an oral multikinase inhibitor, which is structurally similar to sorafenib. It blocks multiple kinases involved in tumour angiogenesis (VEGFR 1-3, Tie2), oncogenesis (KIT, RET, RAF1 and BRAF), and tumour microenvironment (PDGFR and FGFR). In an international multicentre phase III trial (CORRECT), statistically significant, yet modest improvement in OS was demonstrated compared with placebo in patients with colorectal cancer who had failed multiple lines of chemotherapy (6.4 months vs. 5.0 months, hazard ratio = 0.77, 95% confidence interval [CI] = 0.64-0.94, p = 0.0052).[5] The results were similar in a subsequent study targeting Asian populations.[6] However, grade 3 or 4 adverse events (AEs) were high in both trials and in real-world settings,[7] affecting >50% of patients. The modest magnitude of survival prolongation and its significant toxicity suggests the importance of careful patient selection and the urgency of identification of additional treatment strategies. We aimed to review our experience in using regorafenib monotherapy as a last-line treatment, and to investigate predictive markers of treatment response.

METHODS

Patients

This study was approved by the ethics committee of Kowloon Central Cluster/Kowloon Eastern Cluster of the Hospital Authority and conducted in compliance with the Declaration of Helsinki. Records of patients with stage IV colorectal adenocarcinoma who received regorafenib from January 2016 to December 2018 in the Department of Clinical Oncology of Queen Elizabeth Hospital were retrieved and retrospectively analysed. Patients were offered regorafenib after exhausting all available treatments at that time, which included chemotherapy fluoropyrimidine, irinotecan and oxaliplatin; and

biologics with bevacizumab and cetuximab if clinically suitable and affordable.

Treatment

Regorafenib was provided either on a compassionate basis from the pharmaceutical company or as a self-financed item during the study period. Patients received regorafenib 160 mg daily for the first 3 weeks of each 4-week cycle until disease progression, death, intolerable AEs, or patients' refusal to continue / inability to afford treatment. Lower starting doses and dose reduction or escalation during treatment were allowed per clinical judgement of the prescribing physician.

Assessment

Patients were followed up fortnightly with routine monitoring of complete blood counts, liver and renal function tests, and carcinoembryonic antigen (CEA) levels. Interval computed tomography scanning was arranged every 10 to 12 weeks. The RECIST (Response Evaluation Criteria in Solid Tumour) version 1.1 was referred to in order to determine treatment response. AEs were defined and graded according to the CTCAE (Common Terminology Criteria for Adverse Events) version 4.0 by National Cancer Institute. A CEA response was defined as a decrease of CEA from baseline after the start of regorafenib.

Statistical Analyses

Statistical analyses were performed with SPSS (Windows version 26.0; IBM Corp, Armonk [NY], United States). Descriptive statistics on central tendency (e.g., mean, median) and data dispersion (e.g., range, standard deviation, 95% CI) were used. The Kaplan-Meier method and log-rank test were used to depict and analyse survival outcomes. A p value of <0.05 was considered significant.

RESULTS

Patient Characteristics

From January 2016 to December 2018, a total of 14 mCRC patients received regorafenib. Patient baseline characteristics are summarised in Table 1. The median age was 61.3 years. All patients had an Eastern Cooperative Oncology Group (ECOG) performance score of 1. In all, 57.1% of them had primary colon cancer while the rest had primary rectal cancer. In total, 85.7% had liver metastases when regorafenib treatment was initiated, and approximately 60% of them had three or more metastatic sites. Approximately 70% of the patients had K- or N-*Ras* mutant tumours. Half of the patients had undergone anti-VEGF therapy prior to starting regorafenib. In the *Ras* wild-type subgroup, three (75%) of the patients had received an anti-EGFR agent. One patient (25%) chose not to receive anti-EGFR therapy due to affordability. The median number of lines of systemic therapy before regorafenib was two. Only two patients continued onto a next line of treatment after failure of regorafenib. The rest either had died by the time of progression (n = 2), were unfit for further oncological treatment due to disease progression (n = 4), or were unable to afford any more treatment (n = 6).

Table 1. Patient demographics.*

Characteristic	Value
Age, median, years	61.3 (42.1-73)
Sex	
Male	10 (71.4%)
Female	4 (28.6%)
ECOG performance score	
1	14 (100%)
Tumour location	
Colon	8 (57.1%)
Rectum	6 (42.9%)
Sidedness of tumour	
Left-sided	12 (85.7%)
Right-sided	2 (14.3%)
Presence of liver metastases	
Yes	12 (85.7%)
No	2 (14.3%)
K-/N-*Ras* status	
Wild type	4 (28.6%)
Mutant	10 (71.4%)
Previous anti-VEGF exposure	
Yes	7 (50%)
No	7 (50%)
Previous anti-EGFR exposure (*Ras* wild-type only)	
Yes	3 (75%)
No	1 (25%)
Lines of previous treatment, median (range)	2 (2-5)
≤2	9 (64.3%)
>2	5 (35.7%)
CEA response to treatment	11 (78.6%)
Median response	-33.5% (-14% to -73%)
≤50%	7 (63.6%)
>50%	4 (36.4%)
Time to CEA nadir, median (range), days	21 (14-71)

Abbreviations: CEA = carcinoembryonic antigen; ECOG = Eastern Cooperative Oncology Group; EGFR = epithelial growth factor receptor; VEGF = vascular endothelial growth factor.
* Data are shown as No (%), unless otherwise specified.

Response

The median number of cycles of regorafenib received was 2.67. The median dose intensity was 75% of the full dose. Three patients achieved radiographically stable disease, while the 11 others developed progressive disease during regorafenib treatment. The overall

disease control rate was thus 21.4%. At the same time, patients' CEA response was analysed. All patients had baseline CEA elevation (median CEA = 61; range, 8.3-1594). Eleven patients (78.6%) had a drop in CEA after starting regorafenib. The median time to CEA nadir was 3 weeks and the median drop in CEA was 33.5% (range, 14%-73%). Using 50% as a cut-off, which was a value also used in larger studies,[13] seven (63.6%) of the CEA responders had a drop in CEA ≤50%, while four (36.4%) of them had a drop of >50%. No statistically significant correlation was found between the degree of CEA drop and the respective radiological response (Fisher's exact test, p = 1.00).

Tolerance

Average Time to Temporary Treatment Suspension

Ten patients (71.4%) required temporary treatment suspension during their course of regorafenib due to toxicities. The mean total time of suspension was 1.7 weeks, and the mean time of suspension per treatment cycle was 4.9 days.

Adverse Events

Table 2 shows a summary of all the treatment-related AEs. Nine patients (64.3%) experienced toxicity of any kind and grade. Most AEs were severe, with eight patients (57.1%) having grade ≥3 AEs. The most common AEs were palmar-plantar erythrodysaesthesia and fatigue (both 28.6%). Ten patients (71.4%) required suspension at some point in their treatment.

Survival

Progression-free Survival

After a median follow-up of 194 days, disease progression was noted in 13 patients. The median progression-free survival (PFS) was 87 days (95% CI = 81.3-92.6 days). In univariate analysis, PFS was not significantly worse for patients with a lower regorafenib starting dose or who required dose reduction (n = 4), nor was it associated with mean delay per cycle or the mean dose throughout treatment (Table 3). The association between a >50% decrease in CEA and better PFS was not significant (89 vs. 74 days, p = 0.05) [Figure 1].

Overall Survival

The median OS was 186 days (95% CI = 131-241 days). Patients with left-sided tumours had longer OS when compared with those with right-sided tumours (202 vs. 57 days, p = 0.001) [Figure 2]. No other factors were significantly associated with OS (Table 3).

Table 2. Treatment-related adverse events (n = 14).

Adverse events	Any grade	Grade ≥3
Any adverse event	9 (64.3%)	8 (57.1%)
Fatigue	4 (28.6%)	4 (28.6%)
Palmar-plantar erythrodysaesthesia	6 (42.9%)	4 (28.6%)
Diarrhoea	0	0
Hypertension	2 (14.3%)	0
Mucositis	1 (7.1%)	0
Leucopenia	0	0
Thrombocytopenia	1 (7.1%)	0
Proteinuria	2 (14.3%)	0
Hyperbilirubinaemia	1 (7.1%)	1 (7.1%)
Thromboembolic event	1 (7.1%)	0
Gastrointestinal bleeding	2 (14.3%)	1 (7.1%)
Hypertransaminasaemia	2 (14.3%)	0

* Data are shown as No (%).

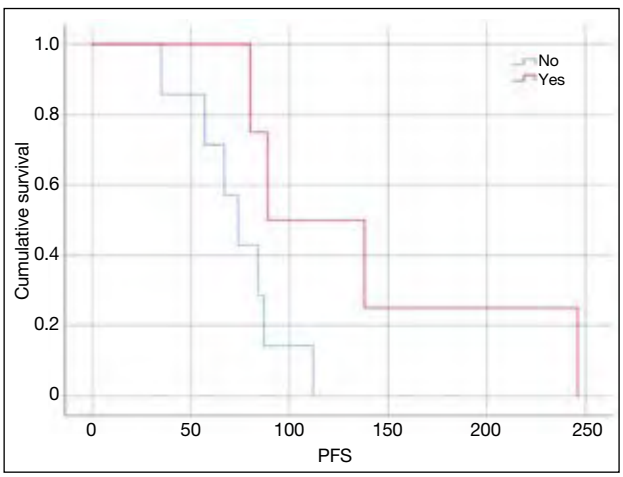

Figure 1. Kaplan-Meier analysis of progression-free survival (PFS) in patients with carcinoembryonic antigen drop >50% from baseline (red line) or ≤50% from baseline (blue line).

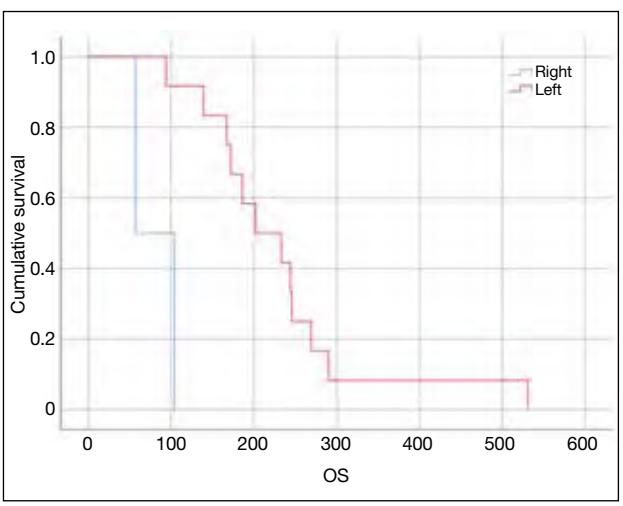

Figure 2. Kaplan-Meier analysis in patients with left- (red line) or right-sided (blue line) primary location.

Table 3. Patient OS and PFS comparison.

Parameters	PFS (days)	p Value	OS (days)	p Value
Median	87.0		186	
Lower starting dose				
Yes	87.0	0.85	139.0	0.32
No	138.0		233.0	
Dose escalation during treatment				
Yes	80.0	0.53	186.0	0.16
No	89.0		172.0	
Dose reduction during treatment				
Yes	89.0	0.84	172.0	0.69
No	84.0		186.0	
Mean dose				
<120 mg	74.0	0.82	172.0	0.85
≥120 mg	87.0		186.0	
Sidedness of tumour				
Left	84.0	0.62	202.0	0.001
Right	35.0		57.0	
RAS status				
Wild type	89.0	0.96	104.0	0.17
Mutant	80.0		202.0	
Previous lines of treatment				
≤2	87.0	0.39	202.0	0.92
>2	74.0		172.0	
Previous anti-VEGF				
Yes	80.0	0.22	167.0	0.17
No	89.0		233.0	
Liver metastases				
Presence	84.0	0.28	172.0	0.43
Absence	62.0		246.0	
No. of metastatic sites				
<3	80.0	0.53	172.0	0.48
≥3	84.0		233.0	
Total time of treatment delay				
≤1 week	74.0	0.11	167.0	0.71
>1 week	112.0		202.0	
CEA drop				
≤50%	74.0	0.05	172.0	0.93
>50%	89.0		202.0	

Abbreviations: CEA = carcinoembryonic antigen; OS = overall survival; PFS = progression-free survival; VEGF = vascular endothelial growth factor.

Subsequent Treatment

Only two (14%) of the patients had satisfactory World Health Organization performance status (i.e., ECOG score 1) and were able to afford and undergo further treatment after disease progression. All of them received trifluridine-tipiracil (Lonsurf; Taiho Oncology, Japan) after regorafenib. Their survivals after regorafenib were 207 and 464 days, respectively.

DISCUSSION

Regorafenib is one of the few treatment options available for mCRC that has failed oxaliplatin- and irinotecan-based chemotherapy. In two large international randomised controlled phase III studies, CORRECT[5] and CONCUR,[6] the median PFS was approximately 60.9 to 91.3 days, and the OS was approximately 197.8 to 273.9 days. In the current study, the median PFS was 87 days (95% CI = 81.3-92.6 days) and the median OS was 186 days (95% CI = 131-241 days), which are comparable to these two phase III studies.

AEs remain a concern in treatment with regorafenib. In both the CORRECT and CONCUR trials, 54% of the patients experienced grade ≥3 AEs,[5,6] which are similar to our study (57.1%). The most common AE in our study was palmar-plantar erythrodysaesthesia, with >40% of patients affected. Approximately two-thirds of these patients had grade ≥3 palmar-plantar erythrodysaesthesia, which commonly led to treatment suspension. Although only 28.6% of the patients experienced fatigue, all of them reported grade 3 fatigue (fatigue limiting self-care) during the course of treatment. The occurrence of fatigue

in trials varies considerably. In the CONCUR trial, only 17% of patients reported fatigue of any grade and only 2.9% had fatigue of grade ≥3.[6] In contrast, 48% of patients experienced fatigue in the CORRECT trial, with 9.6% of them having fatigue grade ≥3.[5] In a systematic review, the incidence of fatigue ranges from 2% to 73% in different studies.[8]

As regorafenib is associated with significant rates of AEs when used at full dose, the optimisation of dosing and schedule is a widely discussed topic. From our data, intercycle delay was common, with >70% of patients experiencing a mean of 4.9 days of delay per treatment cycle due to AEs, but without a statistically significant impact on survival outcome. The PFS and OS for lower starting doses were shorter than those of the usual starting dose, but not significantly shorter. Outcomes also appeared to be independent of dosing strategies (interval dose reduction or interval dose escalation). In ReDOS, a randomised phase II study, patients were randomised to receive a starting dose of 80 mg with subsequent dose escalation, or a standard starting dose of 160 mg. The survival outcomes were not significantly different.[9] While the small sample size limits robust statistical inference, our data concur with the latest evidence. As the slow dose escalation approach appears to result in better tolerability and safety, we expect it to gain popularity in the near future. Other strategies on management of AEs have also been explored, though efficacy is limited. For example, for treatment-related fatigue, one phase II study investigated the effect of dexamethasone on these patients but failed to show any improvement.[10]

Currently there is no established marker to predict the treatment response towards regorafenib. In our study, patients with left-sided tumours enjoyed longer OS, which concurs with the findings of many other studies that left-sided tumours carry a better prognosis regardless of treatment, stage, race of patients, or length of study.[11] Some retrospective studies also suggest that in addition to its prognostic implications, primary tumour location may be a predictive factor for treatment response in the first-line setting.[12] Whether such predictive value also applies to regorafenib warrants further study.

Although not significant, our results showed a marginal association between drop in CEA and PFS. The median time to CEA nadir was found to be 3 weeks. There is no strong evidence on how the degree of CEA decrease correlates with clinical response, and most studies have used arbitrary cut-offs for CEA analysis. We used 50% as an arbitrary cut-off, which was a value also used in larger studies.[13] As most of the CEA responders only achieved stable disease in radiological assessment, it may be suggested that the benefit observed in patients with a drop in CEA of >50% is independent of radiological response. The absolute reading of CEA is known to reflect tumour burden and carries a prognostic value in patients with mCRC, and was reported to have a role in predicting treatment failure in the absence of readily measurable disease response.[14] Further verification is needed in a prospective manner to evaluate its prognostic value.

Treatment beyond regorafenib is limited and no clinical guidelines suggest an agreed-upon next line of treatment, although trifluridine-tipiracil (Lonsurf), the other drug licensed for use in refractory mCRC, is a frequent treatment of choice. In our study, only two patients underwent further treatment with trifluridine-tipiracil, and the survival time was considerably long (median, 400 days). Trifluridine-tipiracil consists of a nucleoside analogue (trifluridine) and a thymidine phosphorylase inhibitor (tipiracil) which causes DNA strand breaks.[15] The different mode of action may explain the longer disease control in patients who have failed regorafenib. Treatment after regorafenib rather than best supportive care is therefore a reasonable option provided that patients are still fit for systemic treatment.

A number of limitations of this study should be acknowledged. First, the eligible population was small (n = 14) as only a proportion of patients remained fit for further treatment after failing multiple lines of chemotherapy. The considerable cost of regorafenib (a self-financed item) also limited the number of eligible patients. As a result, it can only be deduced that there was a tendency suggesting that good response of CEA and a left-sided primary tumour were favourable prognostic factors in patients using regorafenib, and this should be verified in a larger prospective study. Second, the cut-off used for CEA analysis was arbitrary, without verification by prospective data. Finally, the report of toxicity outcomes is also compromised by its retrospective nature and the subjectivity of toxicities like fatigue.

With the advancements in molecular studies, more options will be available for patients with mCRC who have run out of treatment choices. The *BRAF* mutation is found in approximately 5% to 10% of patients with mCRC.[16] It is known to carry a poor prognosis,[17] and is a predictive factor for poor response to anti-EGFR

therapy in *Ras* wild-type patients,[18] so much so that established international guidelines do not recommend anti-EGFR therapy in patients who harbour the *BRAF* mutation.[19] Among these patients, monotherapy with the *BRAF* inhibitor vemurafenib failed to show a meaningful activity in *BRAF*^{V600E}-mutated mCRC.[20] In a phase I/II open-label study, more than half of the study population achieved a stable disease after a combination of the *BRAF* inhibitor dabrafenib, and the *MEK* inhibitor trametinib. The overall response rate was 12% and the median PFS was 3.5 months (95% CI = 3.4-4.0 months).[21] Immune checkpoint inhibitors have been shown to benefit patients with deficient mismatch repair (dMMR), which is characterised by a high number of DNA replication errors and high levels of DNA microsatellite instability. The dMMR tumours are present in approximately 5% of patients with mCRC[22] and are known to carry a poor prognosis, which is driven by its association with the *BRAF* mutation.[17] In a phase II study looking at the use of pembrolizumab in patients with mCRC, an objective response rate (ORR) of 50% was achieved in patients with dMMR, while none was achieved in patients with proficient mismatch repair.[23] OS and PFS have not been reached for patients with dMMR, whereas the OS was 7.6 months and the PFS was 2.3 months for patients with proficient mismatch repair. As a result, pembrolizumab has been granted an indication by the FDA for its use in colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan without satisfactory alternative treatment options. Nivolumab, a monoclonal antibody against programmed cell death protein 1, is another option for patients with dMMR. In the CheckMate 142 trial that looked at nivolumab ± ipilimumab, a monoclonal antibody against cytotoxic T-lymphocyte antigen 4, in heavily pretreated patients with mCRC, the ORR with nivolumab monotherapy was 31.1%.[22] It was even higher in the nivolumab plus ipilimumab group with an ORR of 55%. Grade 3 to 4 toxicities were observed in 20% in the monotherapy group, and 29% in the doublet group.[24] Based on these results, FDA indications have been granted for the use of nivolumab in patients with dMMR who have failed a fluoropyrimidine, oxaliplatin, and irinotecan; and for the use of nivolumab plus ipilimumab for patients with previously treated dMMR mCRC.

In patients with unclear dMMR status, addition of nivolumab to regorafenib has been investigated in REGONIVO, a phase IB study. This strategy yielded an ORR of 38% in the unselected population, and an even higher response in patients with microsatellite instability–high CRC (44%).[25] When used with nivolumab, reduction of the starting dose of regorafenib to 80 mg rendered this regimen more tolerable.

CONCLUSION

Treatments for mCRC after oxaliplatin- and irinotecan-based chemotherapy remain limited. Our institutional experience with regorafenib was generally consistent with the available literature. Our study also found that there is a tendency towards a longer duration of stable disease in patients with an initial drop of CEA after starting regorafenib and a left-sided primary tumour. Treatment beyond regorafenib in those who remain medically fit and are able to afford more treatment resulted in a favourable OS. With the promise of novel agents shown to be highly effective in selected populations, and their overall favourable toxicity profile, further prospective studies are warranted.

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