

Selecting treatment options in refractory metastatic colorectal cancer

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Abstract: Survival of patients with metastatic colorectal cancer (mCRC) has significantly improved in the last decade. Survival gains are not driven by advances in first-line therapy but by incremental additional effects of subsequent treatment lines. To maximize outcomes, patients should receive all active agents. Identification of patient subgroups is increasing individualization of treatment. Novel oral agents, such as regorafenib and TAS-102, as well as promising immunotherapeutic agents have offered salvage treatment options for refractory mCRC. Although most therapeutic developments for mCRC in the chemorefractory setting focuses on new targets and/or more potent agents, reconsideration of established targets has gained importance with the growth of a rational pharmacogenomic approach to drug development, such as HER2. The authors describe treatment options for patients with refractory colon cancer following first- and second-line therapy.

Keywords: TKI, fluoropyrimidine, bevacizumab, cetuximab, panitumumab, PD-1 inhibitor, FOLFIRI, epidermal growth factor receptor, vascular endothelial growth factor receptor, platelet-derived growth factor receptors, KRAS, NRAS, HER2, advanced, colon cancer, refractory, Lonsurf, regorafenib

Introduction

Colon cancer is the third-leading cause of cancer-related death in the USA. In 2018, an estimated 97,000 patients will be diagnosed with colon cancer and 43,000 patients will be diagnosed with rectal cancers; together, colorectal cancer will account for >50,000 deaths.^{1,2} At diagnosis, only 20% of patients have metastatic disease; however, several patients will develop disease progression during the disease course.³ The optimal treatment strategy for patients with nonresectable disease is rapidly changing.

For several years, the backbone of therapy for patients with metastatic colorectal cancer (mCRC) was 5-fluorouracil (5-FU) with leucovorin, which only offered a response rate of ~20% and an overall survival (OS) of 6 months. In the 1990s, oxaliplatin and irinotecan were found to have activity in colon cancer and each drug combined with 5-FU improved OS to nearly 24 months.⁴⁻⁶ In the past several years, the discovery of targeted biologic agents, such as monoclonal antibodies to EGFR and VEGF, targeted kinases, and other cytotoxic agents, in addition to a better understanding of the molecular biology of cancer, have improved OS even further to nearly 30 months.⁷⁻⁹

The National Comprehensive Cancer Network currently recommends that patients with unresectable or metastatic colon cancer receive combination treatment, which usually includes 5-FU with oxaliplatin or irinotecan, in addition to a biologic agent depending on mutation status for first-line therapy.^{10,11} Unfortunately, a large majority of patients develop disease progression or metastatic disease at some point

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following treatment.^{7,12} In summary, the improvement in OS in this patient population represents incremental benefits of later treatments. A strategic approach to therapy is required to optimize patient outcomes. This paper will describe treatment options for patients with refractory colon cancer following first- and second-line therapy. It is important to recognize patients with oligometastatic disease who may benefit from local therapies as opposed to systemic therapies.

Treatment options for refractory metastatic colorectal cancer

The treatment of refractory mCRC includes two new US FDA-approved oral agents: regorafenib approved in 2012 and trifluridine/tipiracil (TAS-102) approved in 2015. Both agents were approved as a single agent in patients with refractory mCRC, each producing modest improvements in OS (Table 1).

Regorafenib

Regorafenib is a multi-targeted tyrosine kinase inhibitor that binds to at least 19 targets, including angiogenic, stromal, and oncogenic tyrosine kinase receptors.^{13,14}

In the CORRECT trial, 760 patients with metastatic colon cancer with disease progression during or within 3 months following standard therapy were randomized to receive regorafenib 160 mg daily or oral placebo daily for 3 of 4 weeks. This study showed that regorafenib improved both progression-free survival (PFS) (1.9 months for regorafenib vs. 1.7 months for placebo, $P<0.0001$) and OS (6.4 months for regorafenib vs. 5.0 months for placebo, $P=0.0052$) for these patients.^{15,16}

Another study, the CONCUR trial, showed similar results in an Asian population. In this study, patients with progressive metastatic disease who had received at least two previous lines of treatment were randomized to regorafenib vs. best supportive care and placebo. This study also showed both a PFS (3.2 months for regorafenib vs. 1.7 months for placebo, $P<0.0001$) and an OS advantage for those who received regorafenib (8.8 months for regorafenib vs. 6.3 months for placebo, $P=0.0002$).¹⁷

Unfortunately, regorafenib led to adverse events in the majority of patients in both the CORRECT and CONCUR trials (93% and 97%, respectively).^{15,17,18} The most common adverse events in patients who received regorafenib in the CORRECT trial were fatigue (67% of patients, 1% of patients with grade 3 or 4 fatigue), hand-foot skin reaction (50% of patients, 21% of patients with grade 3 or 4 hand-foot skin reaction), elevated liver function tests (LFTs) (40%–60%; 8%–13% with grade 3 or 4 elevated LFTs) (Table 2).¹⁵ As a whole, regorafenib can be difficult to tolerate and frequently requires dose modifications. Because of poor tolerability, patients who start regorafenib should have a follow-up appointment with a provider each week to evaluate for the development of adverse events.

For patients who receive regorafenib, it is important that they receive appropriate sequencing of treatment. The REVERCE trial was a phase II trial that evaluated 101 patients with KRAS wild-type (WT) metastatic colon cancer who failed previous therapy. Patients were randomized to regorafenib followed by cetuximab vs. cetuximab followed by regorafenib. This study showed that there is an OS benefit for patients who received regorafenib prior to cetuximab therapy (17.4 months vs. 11.6 months, $P=0.0293$).¹⁹

Table 1 Summary of the efficacy of regorafenib and TAS-102 in refractory metastatic colorectal cancer

Agents	Regorafenib				TAS-102			
Trials	CORRECT ¹		CONCUR ²		RECOURSE ³		TERRA ⁴	
Prior biologics	100% BEV 100% EGFR mAbs		60%		100% BEV 53% EGFR mAbs 18% prior rego		20% BEV 18% EGFR mAbs	
	Rego (n=505)	BSC + PL (n=255)	Rego (n=136)	BSC + PL (n=68)	TAS-102 (n=534)	BSC + PL (n=266)	TAS-102 (n=271)	BSC + PL (n=135)
mOS, mo	6.4	5.0	8.8	6.3	7.1	5.3	7.8	7.1
	HR 0.77 $P=0.0052$		HR 0.55 $P=0.0002$		HR 0.68 $P<0.0001$		HR =0.79 $P=0.0035$	
mPFS, mo	1.9	1.7	3.2	1.7	2.0	1.7	2.0	1.8
	HR 0.49 $P<0.0001$		HR 0.31 $P<0.0001$		HR 0.48 $P<0.0001$		HR =0.43 $P<0.0001$	
RR %	1.0	0.4	4.4	0	1.6	0.4	1.1	0

Abbreviations: bev, bevacizumab; BSC, best supporting care; mAbs, monoclonal antibodies; mo, months; mOS, median overall survival; mPFS, median progression-free survival; PL, placebo; rego, regorafenib.

Table 2 Summary of adverse effects of regorafenib and TAS-102 in refractory metastatic colorectal cancer

Adverse event %	Regorafenib (n=146)		TAS-102 (n=54)		P-value
	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4*	
Hematologic					
Neutropenia	14	3	26	37	<0.0001
Leukopenia	17	2	41	19	0.0001
Anemia	66	9	57	24	0.008
Thrombocytopenia	53	8	33	4	0.52
Nonhematologic					
Nausea	17	0	67	6	0.02
Vomiting	10	0	35	2	0.27
Diarrhea	23	2	28	4	0.61
Fatigue	67	1	78	0	1.00
Anorexia	55	5	69	11	0.21
Mucositis	27	1	31	0	1.00
Hand-foot syndrome	50	21	6	0	<0.0001
Rash	17	4	11	0	0.19
AST increased	60	13	39	0	0.002
ALT increased	43	10	17	0	0.01
Bilirubin increased	40	8	22	0	0.04
Creatinine increased	25	3	11	0	0.33
Febrile neutropenia	NA	0	NA	6	0.02
Fever	32	0	19	0	NA

Note: *Patients also randomized within each treatment arm to receive preemptive or reactive clobetasol for HFSR.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate transaminase; NA, not available.

Alternate dosing of regorafenib

Optimal dosing of regorafenib remains an unanswered question, especially as many patients are required for discontinuing the treatment to maintain the quality of life of the patients. In both the CORRECT and CONCUR trials, patients were treated with the maximum tolerated dose of regorafenib, which may have contributed to the development of adverse events.^{15–17}

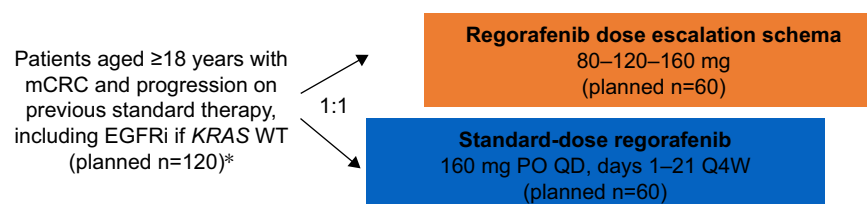
To answer this question, the Regorafenib Dose Optimization Study (ReDOS) was performed. The ReDOS study was a phase II dose-escalation study of regorafenib. In this study, patients were randomized 1:1:1:1 to receive regorafenib 80 mg daily with weekly dose increases if no adverse events vs. regorafenib 160 mg daily without any dose changes, in addition to prophylactic treatment of palmar-plantar-erythroderma (PPE) vs. reactive treatment of PPE (Figure 1). This study met its primary endpoint

of proportion of patients who completed two cycles of protocol treatment and were able to initiate cycle 3 (43% of patients in the escalating dose group vs. 24% in the group who started full-dose therapy, $P=0.0281$). It showed that patients were able to complete more therapy if they were treated with escalating doses as opposed to starting at full dose.²⁰ This suggests that starting a lower dose may increase tolerability of this drug without decreasing effectiveness.

TAS-102: a novel oral fluoropyrimidine

TAS-102 is an orally bioavailable fluoropyrimidine. It consists of two components: trifluridine, a purine analog, and tipiracil, a thymidine phosphorylase inhibitor that helps to prevent the breakdown of trifluridine.^{21,22}

In the RECURSE trial, 800 patients with refractory metastatic colon cancer who had previously received at least

**Figure 1** Schema of the ReDOS for patients with refractory mCRC.

Note: *Patients also randomized within each treatment arm to receive preemptive or reactive clobetasol for HFSR.

Abbreviations: mCRC, metastatic colorectal cancer; ReDOS, Regorafenib Dose Optimization Study; WT, wild-type.

two lines of therapy were randomized in a 2:1 comparison to receive TAS-102 or best supportive care. This study showed that TAS-102 improved PFS (2.0 for TAS-102 vs. 1.7 for placebo, $P<0.0001$) and OS (7.1 months for TAS-102 vs. 5.3 months for placebo, $P<0.0001$).²³

The TERRA study was similar to the RECURSE trial but was performed in an Asian population with metastatic colorectal adenocarcinoma refractory to at least two therapies. Patients were randomized in a 2:1 comparison to TAS-102 vs. best supportive care and placebo. This study also showed the PFS benefit (2.0 months for TAS-102 vs. 1.8 for placebo, $P<0.0001$) and OS benefit for those who received TAS-102 (7.8 months for TAS-102 vs. 7.1 months for placebo, $P=0.0035$).²⁴

Overall, the incidence of adverse events in patients who received TAS-102 was similar to those who received regorafenib; however, adverse events in the TAS-102 group were hematologic in nature: neutropenia (38% of patients) and lymphopenia (21%) (Table 2). Of note, 4% of patients treated with TAS-102 had febrile neutropenia. One patient suffered from treatment-related death due to sepsis. Hematologic toxicity was particularly prevalent among patients who had received multiple lines of therapy. For patients who had previously been treated with at least two lines of therapy, 53% of patients had a cycle delay of at least 4 days due to hematologic toxicity.²³ An additional factor is that TAS-102 has a very complex dosing schedule that requires very detailed and specific dosing instructions.

The C-TASK FORCE study evaluated the efficacy and safety of TAS-102 and bevacizumab in patients with metastatic colon cancer who were refractory or intolerant of previous therapy. In this phase I/II study, patients received two drugs combination per study. Of the 16 patients in the phase II study, 9 did not have progression at 16 weeks, resulting in a 16-week PFS of 42.9%. The most common adverse events were neutropenia (72% of patients), leukopenia (44%), anemia (16%), febrile neutropenia (16%), and thrombocytopenia (12%). Overall, this study showed that TAS-102 with bevacizumab has promising activity and a manageable adverse effect profile, which suggests that this combination may become a potential treatment option for patients with refractory metastatic colon cancer.²⁵

Can we select regorafenib and TAS-102 for the right patient?

Regorafenib and TAS-102 have been tested in very similar situations, but they have not been tested in a head-to-head study.

Sequencing the agents

A retrospective analysis evaluated efficacy and major toxicities associated with both drugs in a Japanese population using propensity score matching. The study found similar efficacy between the agents with regard to tumor response, PFS, and OS, regardless of treatment sequence. However, there were higher rates of dose reductions with regorafenib due to adverse events.²⁶

Similarly, a recent systematic review performed indirect comparison between regorafenib and TAS-102. This study showed similar tumor response, PFS, and OS between the treatment groups. Patients who received regorafenib had a statistically significant increase in all adverse events (RD 0.35, 95% CI: 0.04–0.67, $P=0.013$) and in grade 3–5 adverse events (RD 0.22, 95% CI: 0.13–0.31, $P<0.001$). The subgroup analysis confirmed that regorafenib was associated with higher fatigue and hand–foot syndrome, whereas TAS-102 was associated with more anemia, neutropenia, and thrombocytopenia.²⁷ Sequencing of these drugs should be determined based on patient characteristics and adverse event profiles.

In the RECURSE study, ~20% of patients were previously treated with regorafenib and those who previously received regorafenib had similar response rates to those who had not received regorafenib.²³ This suggests that TAS-102 has similar activity regardless of prior exposure to regorafenib.

In both the CORRECT and RECURSE trials, all patients had previously been exposed to a biologic agent (anti-VEGF or anti-EGFR therapy based on mutation status) prior to treatment with regorafenib or TAS-102.^{15,23} However, in the studies performed in Asia (CONCUR and TERRA studies), only ~40%–50% of patients had been previously exposed to a biologic agent.^{17,24} These studies performed in Asian populations showed very similar outcomes to the CORRECT and RECURSE trials, which suggests that moving regorafenib or TAS-102 to the forefront would not necessarily affect outcomes.^{15,23}

We conclude that both regorafenib and TAS-102 are oral agents that appear to have similar tumor control, PFS, and OS. However, they have not been compared in a head-to-head study. With this in mind, using the adverse event profile can help to guide the appropriate therapies for patients (Table 3). In particular, regorafenib is a reasonable option for patients with good LFTs (Child-Pugh A or B) and good performance status. However, patients who receive regorafenib tend to have more dose reductions due to adverse events; principally, patients who receive regorafenib tend to have higher rates of

Table 3 Hints for when considering salvage therapy for refractory mCRC

Patients may be better off receiving Stivarga® first with:	You want to avoid Lonsurf® in patients with:
1. Good liver function tests (Child-Pugh A and B)	1. Bone marrow reserve issues
2. Good PS	2. Liver function abnormalities (total bilirubin level > 1.5 times the upper limit of normal and any AST level)
3. Exclude MI within 6 months	3. Borderline PS
4. Exclude unstable or new-onset angina	
5. Exclude uncontrolled hypertension	
6. Exclude ATE/VTE within 6 months	

Abbreviations: AST, aspartate transaminase; ATE, aortic thromboembolism; MI, myocardial infarction; PS, performance status; VTE, venous thromboembolism.

hand-foot reaction and fatigue. Alternatively, patients treated with TAS-102 tend to have more difficulty with bone marrow toxicity; specifically, they may not tolerate TAS-102 if they have been heavily pretreated.

Anti-EGFR therapy rechallenge

Another treatment option for patients with refractory metastatic colon cancer is rechallenge with anti-EGFR therapy. In the phase II CRICKET trial, 28 patients with KRAS WT metastatic colon cancer were rechallenged with third-line cetuximab and irinotecan. Six patients had partial response and nine patients had stable disease. This study suggests that patients may benefit from rechallenge with anti-EGFR therapy. In particular, patient selection may be improved by only rechallenging patients who do not develop KRAS mutations.²⁸

Similarly, in the E-Rechallenge trial, 33 patients with KRAS WT mCRC who were refractory to previous fluoropyrimidines, oxaliplatin, irinotecan, cetuximab, and bevacizumab and in whom previous treatment with cetuximab was effective in any earlier line (achieving complete response, partial response, or stable disease that persisted for ≥ 6 months) were rechallenged with cetuximab and oxaliplatin. Overall, 15.6% of the patients had a partial response, 40.6% had stable disease, and 43.8% had progressive disease. Median PFS was 88 days and OS was 262 days. There was no signal for increased adverse events. This study also suggests that patients who have had previous response to anti-EGFR therapy may benefit from rechallenge.²⁹

Immunotherapy to treat mCRC

Another unique subset of colon cancer patients express deficient DNA mismatch repair (dMMR) and a high level of microsatellite instability-high (MSI-h), which is present in ~15% of patients.^{30,31} The presence of MSI-h in patients with metastatic colon cancer is a poor prognostic marker.^{32–35} A histopathologic characteristic is the presence of dense

tumor-infiltrating lymphocytes, which likely contributes to high levels of tumor neoantigens and the corresponding high immunogenicity of these tumors.^{36–41} Early phase studies were performed in patients with 15 different MSI-h cancers, including mCRC. These studies showed an overall objective response rate of 39.6%. Of those who had an objective response, 78% had a response of at least 6 months (range from 1.6 to 22.7 months). In the subset of patients with MSI-h colon cancer, 36% (32/90 patients) had an overall response.^{42–48}

Based upon knowledge of the immunogenic tumor microenvironment in MSI-h tumors, in addition to the observed dramatic response in this subset of patients with anti-PD-1 therapy, a trial of pembrolizumab was undertaken that enrolled three cohorts of patients: MSI-h colorectal cancers, MSI-h noncolorectal cancers, and microsatellite stable colorectal cancers. In this study, patients with MMR-deficient colorectal tumors had an improvement in immune-related overall response rate (40% vs. 0%) and immune-related PFS (78% vs. 11%) compared to patients with MMR-proficient colorectal cancers. Similarly, the PFS (not reached vs. 2.2 months) and OS (not reached vs. 5.0 months) were also improved in the patients with MMR-deficient colorectal cancers compared to patients with MMR proficient colorectal cancer. Of note, patients with MMR-deficient noncolorectal cancers had similar response rates to those with MMR-deficient colorectal cancers.⁴⁴ This study showed that MMR status is predictive of the clinical benefit of pembrolizumab.

Based on positive results in early phase studies, a multi-center, open-label, phase II trial was started to evaluate the role of nivolumab in patients with recurrent or metastatic dMMR/MSI-h colon cancer who had previously been treated with at least one therapy, including fluoropyrimidine and oxaliplatin or irinotecan. Patients were treated with nivolumab 3 mg/kg every 3 weeks for four doses followed by nivolumab 3 mg/kg every 2 weeks until disease

progression, discontinuation because of toxicity, or death. At a median follow-up of 12 months, 23 of 74 patients (31.1%) had a response and 51 of 74 patients (69%) had disease control for ≥ 12 weeks. Median duration of response was not reached. The most common grade 3 or 4 drug-related adverse events were increased concentrations of lipase (8% of patients) and amylase (3% of patients). None of the deaths were deemed to be treatment related by investigators.⁴⁹ This study shows that nivolumab provides durable response rates and disease control in pretreated patients with dMMR colorectal disease.

In the same phase II trial, a subset of patients with dMMR/MSI-h colorectal cancer received ipilimumab 1 mg/kg and nivolumab 3 mg/kg every 3 weeks for four doses followed by nivolumab 3 mg/kg every 2 weeks until disease progression, discontinuation because of toxicity, or death. Of 119 patients, 65 patients (54.6%) achieved an objective response, including 3.4% with complete response and 51.3% with partial response. Disease control for at least 12 weeks was obtained in 95 patients (80%). Any-grade adverse events were reported in 73% of patients, with 49 patients (41%) with grade 1 or 2 events, 32 patients (27%) with grade 3 events, and 6 patients (5%) with grade 4 events. The most common adverse events included fatigue, diarrhea, and pruritis.⁵⁰ This study showed that nivolumab, in addition to ipilimumab, may provide improved efficacy relative to single-agent immune checkpoint blockade without significantly affecting the safety profile.

These studies show that immune checkpoint inhibitors are a promising treatment option for patients with dMMR/MSI-h mCRC.

'Old' target and 'novel' treatment

With a better understanding of the biology and molecular subtypes of colorectal cancer, molecular targeted therapies have emerged as treatment options for patients with metastatic colon cancer.

Approximately 3%–4% of patients with colorectal cancer express HER2 amplifications.^{51,52} In a molecularly annotated platform of patient-derived xenografts, combination therapy of HER2 and EGFR inhibition induced long-lasting tumor regression.⁵³

Based on these results, the HERACLES trial was performed. This was a phase II proof of concept trial that evaluated dual-targeted therapy with trastuzumab and lapatinib in 27 patients with treatment-refractory, KRAS WT, HER2-positive metastatic colon cancer. It showed a median PFS of 21 weeks and a median OS of 46 weeks. In particular, eight patients achieved an objective response rate.

These results are regarded as extraordinary given the heavily pretreated population included in this study (median of five prior regimens). This was the first study to show that there is a genetically defined subpopulation of patients with colorectal cancer (5% of KRAS WT) with sensitivity to pharmacological blockade of a specific oncogenic product. Additionally, the results suggest that the extent of HER2 gene copy number elevation and HER2 expression might be associated with response to treatment.⁵⁴ Further studies are needed to elucidate the role of HER2-directed therapies for colon cancer. Modern biomarkers platforms may also change the landscape of treatment for patients with refractory metastatic colon cancer. These platforms may help to detect new mutations, which may be a target for therapies in the future. Similarly, they may help to direct personalized oncological care.

Conclusion

A significant proportion of heavily pretreated patients with mCRC maintains good performance status and is eligible for further systemic treatment. The survival of patients with metastatic colon cancer has improved significantly in the past decade. These survival gains are not driven by changes in front-line therapy; rather, they represent later stage treatment lines. To maximize outcomes, patients should receive all active treatments if possible. We recognize the importance of personalizing treatment to each individual based on molecular subtyping, in addition to the likelihood of developing adverse effects. Immunotherapies are a promising treatment option that may lead to further survival gains for a subset of patients. Based on this, MSI testing should be considered standard of care for all patients with metastatic colon cancer.

Disclosure

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