Meeting An Unmet Need in Metastatic Colorectal Carcinoma with Regorafenib

Barbara Melosky
British Columbia Cancer Agency, Vancouver, BC, Canada

Corresponding author: Barbara Melosky, MD, FRCPC
Medical Oncologist, BC Cancer Agency
Address: 600- 10th Ave W, Vancouver, BC, V5Z 4E6, Canada
Phone: 604 877 6000; Fax: 604 877 0585
E-mail: bmelosky@bccancer.bc.ca

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ABSTRACT

Colorectal cancer is a global issue, affecting men and women equally. Over the last 25 years, advances in therapy and multidisciplinary care have led to improvements in survival for those with colorectal cancer. Despite these advances, more therapeutic options are needed for those being treated for this disease. Regorafenib is an oral drug that is a new therapeutic option for our patients. The CORRECT and CONCUR trials demonstrate the efficacy of regorafenib in the last line setting.

This article summarizes some of the regorafenib clinical trial data and discusses the strategies to help manage the side effects of this drug including patient education, dose reductions and interruptions, and monitoring hypertension and liver function.

Key words: Metastatic colorectal cancer, oral therapy, overall survival, progression-free survival, regorafenib, side effect management

Introduction

Colorectal cancer affects people worldwide. Globally, 1.2 million new cases of colorectal cancer are diagnosed and approximately 693,900 people die of the disease each year.[1] The disease affects both men and women equally, and is the third most common cancer in men and the second most common in women.[1] Signs and symptoms of colorectal cancer include changes in bowel habits or bowel obstruction, intestinal bleeding/blood in stool, general abdominal discomfort, iron deficiency anemia, weight loss, and decreased appetite.[2] In half of the patients who are diagnosed with colorectal cancer, the disease will metastasize to another site, primarily to the liver, lungs, and lymph nodes.[3]

Drastic survival improvements over the last 25 years

Over the last 25 years, overall survival, defined as the time from official diagnosis of the disease to death, has
dramatically improved for colorectal cancer. In 1992, the Journal of Clinical Oncology reported that overall survival for colorectal cancer was just over 9 months for metastatic colorectal cancer (mCRC) patients treated with the available agents, 5-fluorouracil plus leucovorin.[4] In 2015, overall survival for mCRC patients with a KRAS wild-type status was over 30 months.[5]

Reasons for these dramatic improvements in survival for mCRC patients include new systemic therapies, novel combinations of therapies, multidisciplinary team approaches, improvements in side effect management and better supportive care. Despite this good news, it is important to find more effective treatments. Our patients are often finishing all available lines of therapy, are still well and are requesting further treatments for their disease.

Current treatment options

Treatment goals for patients with mCRC include prolongation of survival, improvement of tumor-related symptoms, arresting tumor progression (disease control) and/or maintaining quality of life.[6] While systemic treatment options for mCRC have increased in the last 20 years, treatment paradigms are still limited. The standard of care differs from one jurisdiction to the next and is dependent on regulatory approval and availability. Generally, all mCRC patients are eligible for two lines of therapy.

Chemotherapy options

Current approved therapy options include chemotherapy and monoclonal antibodies against the vascular endothelial growth factor (VEGF) or the epidermal growth factor receptor (EGFR). Chemotherapy regimens include different combinations of systemic agents including leucovorin (also known as folinic acid or FOL), fluorouracil (F), irinotecan (IRI), oxaliplatin (OX) or capecitabine. The first line therapy regimen for fit patients is usually a combination of agents called FOLFIRI (leucovorin + fluorouracil + IRI) or FOLFOX (leucovorin + fluorouracil + OX). The second line therapy regimen usually includes agents that were not used in the first line. Some countries have approved a combination called FOLFIRINOX (leucovorin + fluorouracil + IRI + OX). This treatment combination essentially combines multiple lines of therapy into one.

Although different countries vary in their lines of therapy, multiple trials have demonstrated that patients who receive the most chemotherapy agents survive the longest.[6]

Monoclonal antibodies against vascular endothelial growth factor and epidermal growth factor receptor

mCRC patients who have RAS wild-type status ("wild-type" means that patients have no identified mutations in either KRAS or NRAS genes) are eligible for an additional line of therapy. Monoclonal antibodies directed against VEGF include bevacizumab and aflibercept, and monoclonal antibodies against EGFR include cetuximab and panitumumab. These monoclonal antibodies bind to their target and inhibit downstream signaling pathways. These monoclonal antibodies are often used in combinations with chemotherapy in the first, second, or third line setting. EGFR-directed monoclonal antibodies are also used as solo agents in the third line setting. Patients who have RAS wild-type status may be offered panitumumab or cetuximab in the third line if they have not received them previously.

The world of RAS mutations

In patients who have a RAS mutation, the RAS protein is constitutively activated and drives the signaling pathway downstream of EGFR. The original EGFR inhibitor trials were conducted in patients who were not selected on the basis of whether or not their tumors contained RAS mutations. Retrospective mutation analysis of these early trials has revealed that the EGFR inhibitors cetuximab or panitumumab are only efficacious in patients whose tumors did not harbor KRAS gene mutations.[7-11] Further studies have shown that RAS mutations emerge during anti-EGFR therapy.[12-14]

We originally estimated that up to 40% of our patients with mCRC had a KRAS mutation and thus were not eligible for cetuximab or panitumumab. This meant that more than 60% of patients were able to derive a possible benefit from anti-EGFR antibodies. Recently we discovered additional mutations in the KRAS and NRAS genes, which are detected in an additional 10-20% of mCRC patients. Not surprisingly, patients whose tumors have any of these mutations also do not respond to the anti-EGFR antibodies cetuximab and panitumumab. As a result of these additional mutations, the population of mCRC patients eligible for EGFR-inhibitors is diminishing. Now, less than 50% of mCRC patients are eligible for cetuximab or panitumumab, either alone or in combination as part of first, second, or third line of care [Figure 1].[15] As RAS mutation testing becomes more sensitive and more mutations are discovered, we anticipate that even fewer patients will be eligible for anti-EGFR treatment.

In addition to the shrinking number of patients who are candidates for EGFR-inhibitors, the new therapy
combinations condense multiple therapy lines into one. Until recently, options for patients who complete all available treatment options and still have a good performance status were limited and included best supportive care, participation in a clinical trial, or the use of any chemotherapy strategy not tried yet. There is a need for more options for fit mCRC patients who have exhausted all other lines of therapy.

**Regorafenib: A Treatment Option for mCRC**

Regorafenib is a relatively new multi-kinase inhibitor that simultaneously affects a number of different pathways that are involved in cancer development and progression. This includes anti-angiogenic pathways including VEGFR1-3 and TIE2, stromal pathways such as platelet-derived growth factor receptor (PDGFR), fibroblast growth factor receptor, and oncogenic drivers KIT, PDGFR, and RET. While the treatment goal of chemotherapy is to reduce tumor size, the goal of targeted therapies such as regorafenib is to stop or delay disease progression. Regorafenib has recently demonstrated efficacy in two randomized clinical trials, CORRECT and CONCUR.

**The CORRECT and CONCUR trials**

CORRECT and CONCUR trials were randomized, phase III trial conducted in mCRC patients who had failed all standard lines of therapy. The study designs of the two trials were similar and are compared in Figure 2. CORRECT accrued very rapidly, in only 9 months, confirming an unmet need in patients who have progressed on all therapy. The CONCUR trial was conducted to confirm the regorafenib efficacy results from the CORRECT trial, but differed in that prior anti-VEGF or anti-EGFR targeted therapy was permitted, but not mandatory.

Both trials met their primary endpoint of overall survival [Figure 3]. In the final updated analysis of the CORRECT trial, patients who were randomized to regorafenib had a median overall survival of 6.4 months (95% confidence interval [CI], 5.8-7.0) versus 5.0 months (95% CI, 4.4-5.9) for patients given a placebo (hazard ratio [HR] 0.79; 95% CI, 0.66-0.94; P = 0.0038). In the CONCUR trial, patients randomized to regorafenib had a median overall survival of 8.8 months versus 6.3 months for patients given a placebo (HR 0.550, 95% CI 0.40-0.77, P = 0.00016). As illustrated in Figure 3, the overall survival curves from both trials split quickly and stayed apart, demonstrating the beneficial effect of regorafenib in this treatment-refractory population.

A secondary endpoint of both trials was progression-free survival, defined as the time from date of randomization to date of progression or death (whatever occurs earlier). This secondary endpoint was also met in both trials. The curve split at when the first computed tomography scan was done, at the 50-day mark [Figure 4]. In the CORRECT trial, the progression-free survival of patients on regorafenib was 1.9 months as compared to 1.7 months for patients who were on placebo (HR 0.49, 95% CI, 0.42-0.58, P > 0.0001). The progression-free survival of patients on regorafenib in the CONCUR trial was 3.2 as compared to 1.7 months on placebo (HR 0.31, 95% CI 0.22-0.44, P < 0.0001). This amounted to a 69% reduction in risk of progression or death in the regorafenib group.

Other secondary endpoints of these trials included objective response rates and disease control rates. Regorafenib not only significantly improved disease control rates compared with placebo, but the quality of life of patients on regorafenib in both trials did not deteriorate, but was

![Figure 1: Distribution of RAS mutations in metastatic colorectal cancer then and now](image1)

![Figure 2: Study design for CORRECT and CONCUR trials](image2)
equal to the quality of life of patients in the placebo arm. These results are impressive, especially in a group that is heavily pretreated and progressing. Importantly, which patients benefitted most from regorafenib? A subgroup analysis of the CORRECT trial showed that almost all patient groups benefited from the regorafenib, regardless of gender, age, location (North America, Europe, Asia, and Australia), performance status or primary disease site (colon or rectum), whether their first diagnosis of metastatic disease to randomization was less or greater than 18 months or their prior anti-cancer treatment. The one exception was the group of patients with primary disease in both colon and rectum and was based on only a few events.

In addition, the \( KRAS \) mutation status of all patients was analyzed, and was found to be neither prognostic nor predictive. Patients in both the \( KRAS \) wild-type and mutation subgroups experienced benefits in overall survival and progression-free survival. All patients, regardless of prior treatment or \( RAS \) status, can benefit from this treatment.

**Summary: Regorafenib efficacy**

The CORRECT and CONCUR trials demonstrated that regorafenib is an important therapy for patients who have progressed after all standard therapy. An overall survival difference of 6.4 months for regorafenib compared with 5.0 months for placebo in CORRECT (and 8.8 vs. 6.3 months in CONCUR) is clinically meaningful, especially when there is no other standard treatment options exit for patients who have a good performance status and would like further treatment. The observed gain in survival was a median value; in clinical practice, many patients on regorafenib have prolonged survival. Regorafenib increased the overall survival in patients who are progressing with metastatic cancer after standard therapy. This should now become the new standard of care in this patient population.
Patient Management Strategies for Regorafenib

In CORRECT, Grade 3 or 4 treatment-related adverse events occurred in 54% of patients randomized to regorafenib as compared to 14% of patients randomized to placebo.[16] The most common adverse events related to regorafenib compared to placebo in the CORRECT trial included hand–foot skin reaction (17% vs. <1%), fatigue (10% vs. 6%), diarrhea (8% vs. 1%), hypertension (7% vs. 1%) and rash/desquamation (6% vs. 0%).[16] Regorafenib-related side effects of the CONCUR trial included hand–foot skin reaction (16% vs. none), hypertension (11% vs. 3%), hyperbilirubinemia (7% vs. 1%), hypophosphatemia (7% vs. none), alanine aminotransferase (ALT) concentration increases (7% vs. none), aspartate aminotransferase (AST) concentration increases (6% vs. none).[17]

Patient education and management strategies

Patient education is an important feature of side effect management. We need to educate our patients about hand–foot syndrome and other adverse events and teach them to call the treating physician or nurse with any complications they may experience.

There are a number of supportive measures that care
providers can recommend to patients, including coaching patients to modify their activities of daily living [Table 1].

| Table 1: Management strategies for hand–foot skin reactions |
|-------------------------------------------------------------|
| **Aim** | **Strategy** |
| Cushion and protect hands and feet | Avoid tight socks |
| | Wear well-padded footwear |
| | Use insole cushions or inserts in shoes |
| | Avoid walking long distances |
| | Prevent secondary infection by keeping hands and feet clean |
| | Avoid hot water |
| | Foot soaks with tepid water and Epsom salts |
| | Use a moisturizing cream after bathing |
| | Use socks/gloves to cover moisturizing cream |
| Control of calluses | Before initiating regorafenib treatment |
| | Check condition of hands and feet |
| | Have a manicure and pedicure prior to treatment |
| | Exfoliate rough spots with pumice stone |
| | During regorafenib treatment |
| | Avoid pressure points |
| | Avoid items that rub, pinch or create friction |
| Use of creams | General protection |
| | Early, continuous and liberal use of nonurea-based creams |
| | Examples: Cetaphil, aveeno, udderly smooth, gold bond, Norwegian formula, eucerin |
| | Hyperkeratotic lesion treatment |
| | Apply keratolytic creams (urea-based creams and salicylic acid 6%) sparingly and only to affected (hyperkeratotic) areas |
| | Gentle exfoliation |
| | Apply alpha hydroxy acids-based creams (5–8%) liberally 2 times each day |
| | Discomfort, pain, inflammation |
| | Topical corticosteroids (clobetasol 0.05%) or topical analgesics (lidocaine 2%), oral analgesics if needed |

Patients should be advised to avoid tight socks, to wear well-padded footwear with insole cushions or inserts, and to avoid walking long distances. Patients should be advised to prevent secondary infection by keeping hands and feet clean, to avoid hot water, use tepid water and Epson salts for foot soaks. They should be advised to use moisturizing creams after bathing and use socks and gloves to protect hands covered in moisturizing cream. Patient should be taught how to control calluses before and during regorafenib treatment and should be advised about the use of creams to alleviate various symptoms.

### Regorafenib dose reductions

Dose modifications are an important strategy for managing regorafenib-related side effects. Regorafenib is an oral tablet that comes in a 40-mg dose. Patients in the CORRECT trial were started on 160 mg, or four tablets/day. If necessary, this could be reduced to 120 mg (three tablets) or to 80 mg (two tablets)/day [Table 2]. Treating physicians and nurses should not be afraid to modify or interrupt the dose of regorafenib to improve the side effect profile. Dose reduction strategies for regorafenib-related toxicities, hand-foot syndrome and hypertension are shown in Tables 3-5. Many patients will need a dose reduction and can continue on therapy without a detriment of their quality of life.

### Monitoring blood pressure

As regorafenib can lead to hypertension, blood pressure should be monitored weekly for the first 6 weeks of treatment and reported to the treating physician if it is out of normal range (diastolic \( \geq 100 \text{ mmHg} \) and systolic \( \geq 150 \text{ mmHg} \), or a \( \geq 20 \text{ mmHg} \) increase in diastolic measurement if the measurement was previously within normal limits).

### Monitoring liver function

As regorafenib can affect liver function, we need to monitor liver enzymes. ALT, AST, and bilirubin are all important laboratory parameters to be ordered on a regular basis. A dose reduction or interruption may be necessary to manage liver-related side effects.

| Table 2: Standard and reduced regorafenib dose levels |
|------------------------------------------------------|
| **Dose level** | **Dose (mg/day)** | **Tablets** |
| Level 0 (standard dose) | 160 | 4 |
| Level 1 | 120 | 3 |
| Level 2 | 80 | 2 |

| Table 3: Dose modifications for regorafenib-related toxicities except hand–foot skin reaction and hypertension* |
|--------------------------------------------------------------|
| **NCI CTC version 3.0** | **Dose interruption** | **Dose modification** | **Dose for subsequent cycles** |
| Grade 0/2 | Treat on time | Level 0 (no change) | Level 0 (no change) |
| Grade 3 | Delay until < Grade 2 | Level 1 (reduce by 1 dose level) | If toxicity remains < Grade 2, dose re-escalation can be considered at the discretion of the treating investigator. If dose is re-escalated and toxicity (\( \geq \) Grade 3) recurs, institute permanent dose reduction |
| Grade 4 | Delay until < Grade 2 | Level 1 (reduce by 1 dose level) | Permanent discontinuation can be considered at treating investigator’s discretion |

*Table adapted from CORRECT protocol. Excludes alopecia, nonrefractory nausea/vomiting, nonrefractory hypersensitivity and asymptomatic laboratory abnormalities. *If no recovery after a 4 week delay, treatment will be permanently discontinued. NCI: National Cancer Institute, CTC: Common Toxicity Criteria.
Table 4: Dose modification for hand–foot skin reaction

| Skin toxicity grade | Description                                                                 | Occurrence         | Suggested dose modification                                                                 |
|---------------------|-----------------------------------------------------------------------------|--------------------|-------------------------------------------------------------------------------------------|
| Grade 1             | Numbness, dysesthesia, paraesthesia, tingling, painless swelling, erythema or discomfort of the hands or feet which does not disrupt the patient’s normal activities | Any                | Maintain dose level and supportive measures                                                  |
| Grade 2             | Painful erythema and swelling of the hands or feet and/or discomfort which affects the patient’s normal activities | First occurrence  | Consider 1 dose level reduction and supportive measures                                      |
|                     |                                                                             | No improvement ≤ 7 days or second occurrence | If no improvement - interrupt dose (7 days min) until resolves to Grade 0–1*               |
|                     |                                                                             | Third occurrence  | Interrupt dose until resolves to Grade 0–1                                                  |
|                     |                                                                             | If no improvement ≤ 7 days until resolves to Grade 0–1* | Resume at decreased dose level*                                                              |
|                     |                                                                             | Fourth occurrence | Discontinue therapy                                                                          |
| Grade 3             | Moist desquamation, ulceration, blistering or severe pain of the hands or feet, or severe discomfort that causes the patient to be unable to work or perform activities of daily living | First occurrence  | Supportive measures                                                                          |
|                     |                                                                             | Second occurrence | Interrupt dose (7 days min) until resolves to Grade 0–1                                      |
|                     |                                                                             | If diastolic BP is not controlled (≤ 100 mmHg) with the addition of new therapy, reduce one dose level* | Resume at decreased dose by 1 additional level*                                              |
|                     |                                                                             | Third occurrence  | Discontinue therapy                                                                          |
|                     | Table adapted from CORRECT protocol. *If toxicity returned to Grade 0–1 after dose reduction. Dose re-escalation was permitted at the discretion of the investigator |

Table 5: Management of regorafenib-emergent hypertension

| Grade of event (CTCAE version 3.0) | Description                                                                 | Management                                                                 |
|------------------------------------|-----------------------------------------------------------------------------|---------------------------------------------------------------------------|
| Grade 1                            | Asymptomatic Grade 2: Recurrent or persistent (≤ 24 h) increase by > 20 mmHg (diastolic) or to > 150/100 | Increase frequency of blood pressure monitoring                           |
| Grade 2                            | Symptomatic Grade 2: Any increase by > 20 mmHg (diastolic) or to > 150/100, associated with symptoms | Begin anti-hypertensive therapy and continue regorafenib                  |
|                                   |                                                                             | If diastolic BP is not controlled (≤ 100 mmHg) with the addition of new therapy, reduce one dose level* | Hold regorafenib until symptoms resolve and diastolic BP ≤ 100 mmHg; also treat subject with anti-hypertensive medications |
|                                   |                                                                             | If diastolic BP is not controlled (≤ 100 mmHg) with the addition of new therapy, reduce one dose level* | When regorafenib is restarted, reduce by one dose level* |
| Grade 3                            |                                                                             | Hold regorafenib until symptoms resolve and diastolic BP ≤ 100 mmHg and increase current anti-hypertensive medication(s)/add additional anti-hypertensive medications | Discontinue therapy |
| Grade 4                            |                                                                             | Increase current anti-hypertensive medication(s)/add additional anti-hypertensive medications |                                                                             |
|                                   |                                                                             | When regorafenib is restarted, reduce by one dose level*                  |                                                                             |
|                                   |                                                                             | If diastolic BP is not controlled (≤ 100 mmHg) with the addition of more intensive therapy, reduce another dose level* |                                                                             |
|                                   | Table adapted from CORRECT protocol. *BP remains controlled for at least one full cycle, dose re-escalation is permitted at the investigator’s discretion. **Subjects requiring a delay of ≥ 4 weeks should go off therapy. |                                                                             |

Conclusion

Patients with mCRC are now living longer than ever before. Treatment for mCRC continues to evolve. Fewer patients are eligible for EGFR inhibitors due to the discovery of RAS mutations. This has resulted in an unmet need for fit patients who have exhausted all lines of therapy. Regorafenib is a therapy option in patients with mCRC in the end-of-line treatment setting. Despite adverse events experienced during treatment, patients treated with regorafenib can expect increased survival as well as a delayed time to deterioration in health status. As an oral drug, side effects can be managed with patient education and coaching and proper dose reductions.

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Conflicts of interest

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Bristol-Myers Squibb, Novartis, Astra Zeneca. She has served as a consultant/advisory role with Boehringer Ingelheim and her institute has received research funding from Roche and Bayer.

References

1. Global Cancer Facts & Figures. 3rd ed. Available from: http://www.cancer.org/acs/groups/content/@research/documents/document/acspc-044738.pdf. [Last accessed on 2015 Sep 29].
2. Canadian Cancer Society’s Advisory Committee on Cancer Statistics. Canadian Cancer Statistics 2015. Toronto, ON: Canadian Cancer Society; 2015.
3. Wei EK, Wolin KY, Colditz GA. Time course of risk factors in cancer etiology and progression. J Clin Oncol 2010;28:4052-7.
4. Venook AP, Niedzwiecki D, Lenz HF, Innocenti F, Mahoney MR, O’Neil BH, et al. CALGB/SWOG 80405: Phase III trial of irinotecan/5-FU/leucovorin (FOLFIRI) or oxaliplatin/5-FU/leucovorin (mFOLFOX6) with bevacizumab (BV) or cetuximab (CET) for patients (pts) with KRAS wild-type (wt) untreated metastatic adenocarcinoma of the colon or rectum (MCRC). J Clin Oncol 2014;32 (suppl; abstr LBA3):5s.
5. 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 Suppl 3:iii1-9.
6. Grothey A. Optimizing systemic therapy selection in metastatic colorectal cancer. J Natl Compr Canc Netw 2015;13 (5 Suppl):682-5.
7. Amado RG, Wolf M, Peeters M, Van Cutsem E, Siena S, Freeman DJ, et al. Wild-type KRAS is required for panitumumab efficacy in patients with metastatic colorectal cancer. J Clin Oncol 2008;26:1626-34.
8. Karapetis CS, Khambata-Ford S, Jonker DJ, O’Callaghan CJ, Tu D, Tebbutt NC, et al. K-ras mutations and benefit from cetuximab in advanced colorectal cancer. N Engl J Med 2008;359:1757-65.
9. Douillard JY, Siena S, Cassidy J, Taberner J, Burkes R, Barigel M, et al. Randomized, phase III trial of panitumumab with infusional fluorouracil, leucovorin, and oxaliplatin (FOLFOX4) versus FOLFOX4 alone as first-line treatment in patients with previously untreated metastatic colorectal cancer: The PRIME study. J Clin Oncol 2010;28:4697-705.
10. Douillard JY, Oliner KS, Siena S, Taberner J, Burkes R, Barigel M, et al. Panitumumab-FOLFOX4 treatment and RAS mutations in colorectal cancer. N Engl J Med 2013;369:1023-34.
11. Jonker DJ, O’Callaghan CJ, Karapetis CS, Zalcberg JR, Tu D, Au HJ, et al. Cetuximab for the treatment of colorectal cancer. N Engl J Med 2007;357:2040-6.
12. Diaz LA Jr, Williams RT, Wu J, Kinde I, Hecht JR, Berlin J, et al. The molecular evolution of acquired resistance to targeted EGFR blockade in colorectal cancers. Nature 2012;486:537-40.
13. Misale S, Yaeger R, Hobor S, Scala E, Janakiraman M, Liska D, et al. Emergence of KRAS mutations and acquired resistance to anti-EGFR therapy in colorectal cancer. Nature 2012;486:532-6.
14. Vilar E, Taberner J. Cancer: Pinprick diagnostics. Nature 2012;486:482-3.
15. Sorich MJ, Wiese MD, Rowland A, Kichenadasse G, McKinnon RA, Karapetis CS. Extended RAS mutations and anti-EGFR monoclonal antibody survival benefit in metastatic colorectal cancer: A meta-analysis of randomized, controlled trials. Ann Oncol 2015;26:13-21.
16. Grothey A, Van Cutsem E, Sobrero A, Siena S, Falcone A, Ychou M, et al. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): An international, multicentre, randomised, placebo-controlled, phase 3 trial. Lancet 2013;381:303-12.
17. Li J, Qin S, Xu R, You TC, Ma B, Pan H, et al. Regorafenib plus best supportive care versus placebo plus best supportive care in Asian patients with previously treated metastatic colorectal cancer (CONCUR): A randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 2013;381:303-12.
18. Taberner J, Lenz HJ, Siena S, Sobrero A, Falcone A, Ychou M, et al. Analysis of circulating DNA and protein biomarkers to predict the clinical activity of regorafenib and assess prognosis in patients with metastatic colorectal cancer: A retrospective, exploratory analysis of the CORRECT trial. Lancet Oncol 2015;16:937-48.
19. Chang J, Powar V, Grothey A, Sobrero A, Siena S, Falcone A, et al. Time to Health Status Deterioration in Regorafenib-treated Patients with Metastatic Colorectal Cancer (mCRC): A Post-hoc Analysis of the Phase III CORRECT Study. Presented at the European Cancer Congress, Amsterdam, The Netherlands;2013.