

A Closer Look at Targeted Therapies in Metastatic Colorectal Cancer

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Summary

The discovery of key regulators in cancer cell growth has led to the development of targeted therapies in many cancers, including colorectal cancer. Five targeted therapies are now approved for use in metastatic colorectal cancer (mCRC). These therapies modestly increase overall survival and progression-free survival in a heavily pretreated patient population.

Key Points

- Targeted therapy combined with chemotherapy is the standard of care in mCRC.
- EGFR inhibitors are beneficial in patients without KRAS mutations.
- VEGF inhibitors are beneficial in both KRAS mutated and wild-type patients.
- There are no head-to-head trials to identify the most effective or safest targeted therapy.
- The choice of targeted therapy in mCRC depends both on underlying mutations and previous therapy.
- Data support continuing antiangiogenic therapies beyond progression.

THE DISCOVERY OF EPIDERMAL GROWTH factor receptor (EGFR) and vascular endothelial growth factor (VEGF), two key regulators of tumor cell growth, survival, metastasis, and angiogenesis, has led to the development of targeted biologic therapies for colorectal cancer. Five targeted therapies have been approved for use in metastatic colorectal cancer (mCRC) in combination with chemotherapy. Bevacizumab (Avastin[®]), ziv-aflibercept (Zaltrap[®]), and regorafenib (Stivarga[®]) all target VEGF. Cetuximab (Erbix[®]) and panitumumab (Vectibix[®]) are EGFR inhibitors.

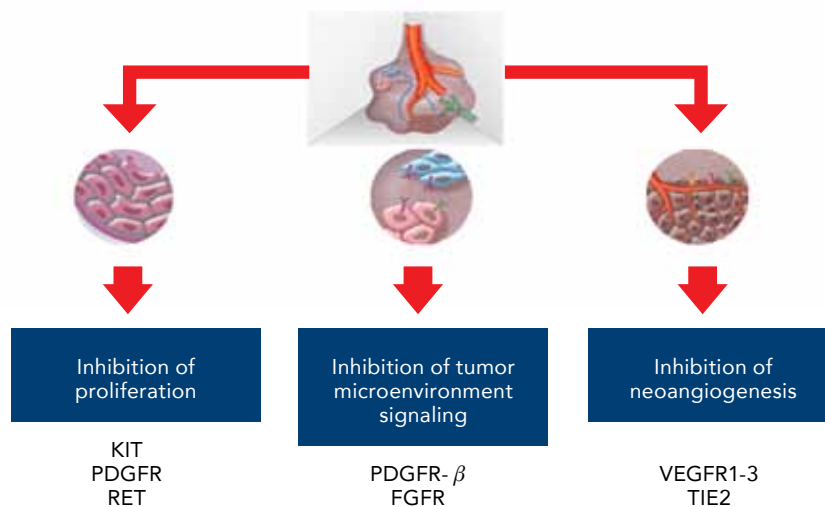
Bevacizumab was the first VEGF inhibitor approved by the FDA. In the trials used to get this agent approved, the addition of bevacizumab to chemotherapy improved overall survival (OS) by 4.4 months compared with placebo in mCRC (20.3 months vs 15.6 months).¹ There is still an improve-

ment in survival even out to two years. There are data to support combining bevacizumab with single agent, doublet, or triplet chemotherapy. Thus, depending on the patient's ability to tolerate chemotherapy, bevacizumab still adds survival benefit. There are also data demonstrating benefits of continuing bevacizumab even when the patient's cancer has progressed.^{2,3}

Aflibercept is a fusion protein of key domains from human VEGF receptors 1 and 2 with constant region (Fc) of human immunoglobulin G.⁴ It blocks all human VEGF-A isoforms, VEGF-B, and placental growth factor (PlGF).⁵ It binds VEGF-A and PlGF more tightly than native receptors. Because it has a different mechanism of action than bevacizumab, it hits more targets, which may be a possible benefit.

In the main study used for FDA approval, afliber-

Exhibit 1: Regorafenib Mechanism of Action⁷⁻⁹



KIT = V-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog
 RET = rearranged during transfection proto-oncogene
 PDGFR = platelet-derived growth factor receptor
 FGFR = fibroblast growth factor receptor
 VEGFR = vascular endothelial growth factor receptor
 TIE2 = TEK tyrosine kinase, endothelial

cept was studied in combination with FOLFIRI (leucovorin, 5-fluorouracil (5-FU), and irinotecan (Camptosar). Addition of aflibercept increased OS by a median of 1.4 months.⁶ The hazard ratio (HR) was 0.82 so the people who received aflibercept had a 20 percent lower likelihood of death during the trial. It also increased progression-free survival by 2.2 months. It had similar effects whether patients were previously treated with bevacizumab or not (PFS difference 2.8 months, OS difference 0.8 months). Addition of this agent to standard chemotherapy does result in higher rates of certain adverse effects including hypertension, hemorrhage, proteinuria, and thromboembolic events, which are common adverse effects of VEGF inhibition. It has not been compared to bevacizumab in a trial.

Regorafenib is another new targeted therapy approved for mCRC. This is an oral multikinase inhibitor that targets multiple areas of tumor growth including VEGF (Exhibit 1).⁷⁻⁹ Regorafenib has been studied in combination with best supportive care in patients with mCRC who have progressed after standard therapy.¹⁰ The target population for this study were those with disease progression during or within three months after last administration of or intolerance to approved standard therapies, which had to include fluoropyrimidine, oxaliplatin, irinotecan, bevacizumab, and cetuximab or

panitumumab. This was a very treatment-resistant study group. Addition of regorafenib improved OS by median 1.4 months and PFS by 0.2 months. The most common adverse effects of this agent are hand-foot skin reaction, rash, fatigue, hypertension, diarrhea, and voice change. Voice changes occur in about 30 percent of patients treated with VEGF inhibiting agents.

Certain genetic mutations have been identified in colorectal cancer. One of these is in the KRAS (V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog) gene. The protein product of the normal KRAS gene performs an essential function in normal tissue signaling, and the mutation of a KRAS gene is an essential step in the development of many cancers. Since KRAS can be used to predict outcomes of therapy, patients should be tested for KRAS mutations before treatment.

The story with KRAS mutation and response to therapy is different for the VEGF and EGFR inhibitors. KRAS mutation status does not have an impact on VEGF inhibitor efficacy but does for the EGFR inhibitors.

Cetuximab and panitumumab block the EGFR receptor. Around 40 percent of patients with colorectal cancer have KRAS mutations that bypass the EGFR receptor. In patients with these mutations, there is no benefit of adding an EGFR inhibi-

Exhibit 2: KRAS as Biomarker for Panitumumab Response in mCRC¹⁵

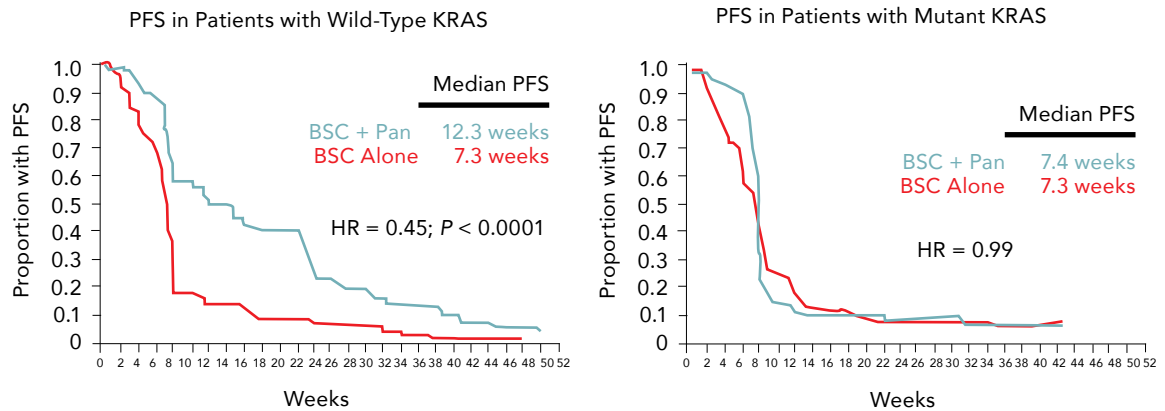


Exhibit 3: How Best to Use the Targeted Agents

KRAS Wild-Type Disease

- First Line
 - Oxaliplatin-based regimen: Bevacizumab plus XELOX or FOLFOX
 - Irinotecan-based regimen: Bevacizumab plus FOLFIRI or EGFR I plus FOLFIRI
- Second Line and Beyond
 - FOLFIRI/ EGFR I in first line
 - FOLFOX/Bevacizumab
 - Third line: Regorafenib
 - FOLFIRI/Bev in first line
 - Second/Third line
 - FOLFOX/Bev
 - Irinotecan/EGFR 1
 - Fourth line: Regorafenib
 - FOLFOX/ Bev in first line
 - Second line
 - FOLFIRI/Bev
 - FOLFIRI/Aflibercept
 - Third line: Irinotecan/EGFR I
 - Fourth line: Regorafenib

KRAS Mutated Disease

- First Line
 - FOLFIRI/Bev
 - FOLFOX/Bev
- Second Line
 - FOLFOX/Bev in first line
 - FOLFIRI/Bev
 - FOLFIRI/Aflibercept
 - FOLFIRI/Bev in first line
 - FOLFOX/Bev
- Third Line
 - Regorafenib

Bev = bevacizumab; XELOX = capecitabine/oxaliplatin; EGFR I = endothelial growth factor inhibitor; FOLFIRI = 5-FU/leucovorin/irinotecan; FOLFOX = 5-FU/leucovorin/oxaliplatin

tor in those with KRAS mutation.¹¹⁻¹⁵ As shown in Exhibit 2, EGFR inhibitors provide significant benefit in those with wild-type KRAS and no benefit in those with mutant KRAS.¹⁵

There are many different options for managing

mCRC with combinations of chemotherapy and targeted agents and, in some cases, monotherapy with targeted agents. Exhibit 3 shows the treatment options for first-line and subsequent lines of therapy dependent on KRAS status.

Conclusion

Targeted therapy combined with chemotherapy has become the standard of care in mCRC. There are now several antiangiogenic therapies that target VEGF, but it is not known which is best because they have not been compared head-to-head. There are data to support continuing them beyond progression. EGFR inhibitors provide benefit for patients who do not have KRAS mutations. Importantly, KRAS mutation status does not impact antiangiogenic therapy outcome. There is a need for better biomarkers to decide on how best to select the targeted agents.

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References

1. Hurwitz H, Fehrenbacher L, Novotny W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. *N Engl J Med*. 2004;350(23):2335-42.
2. Bennouna J, Sastre J, Arnold D, et al. Continuation of bevacizumab after first progression in metastatic colorectal cancer (ML18147): a randomised phase 3 trial. *Lancet Oncol*. 2014;14(1):29-37.
3. Kubicka S, Greil R, André T, et al. Bevacizumab plus chemotherapy continued beyond first progression in patients with metastatic colorectal cancer previously treated with bevacizumab plus chemotherapy: ML18147 study KRAS subgroup findings. *Ann Oncol*. 2013;24(9):2342-9.
4. Holash J, Davis S, Papadopoulos N, et al. VEGF-Trap: a VEGF blocker with potent antitumor effects. *Proc Natl Acad Sci U S A*. 2002;99(17):11393-8.
5. Tew WP, Gordon M, Murren J, et al. Phase 1 study of aflibercept administered subcutaneously to patients with advanced solid tumors. *Clin Cancer Res*. 2010;16(1):358-66.
6. Van Cutsem E, Tabernero J, et al. Addition of aflibercept to fluorouracil, leucovorin, and irinotecan improves survival in a phase III randomized trial in patients with metastatic colorectal cancer previously treated with an oxaliplatin-based regimen. *J Clin Oncol*. 2012;30(28):3499-506.
7. Wilhelm SM, Dumas J, Adnane L, et al. Regorafenib (BAY 73-4506): a new oral multikinase inhibitor of angiogenic, stromal and oncogenic receptor tyrosine kinases with potent preclinical antitumor activity. *Int J Cancer*. 2011;129(1):245-55.
8. Mross K, Frost A, Steinbild S, et al. A phase I dose-escalation study of regorafenib (BAY 73-4506), an inhibitor of oncogenic, angiogenic, and stromal kinases, in patients with advanced solid tumors. *Clin Cancer Res*. 2012;18(9):2658-67.
9. Strumberg D, Schultheis B. Regorafenib for cancer. *Expert Opin Investig Drugs*. 2012;21(6):879-89.
10. Grothey A, Van Cutsem E, Sobrero A, et al. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. *Lancet*. 2013;381(9863):303-12.
11. Lièvre A, Bachet JB, Boige V, et al. KRAS mutations as an independent prognostic factor in patients with advanced colorectal cancer treated with cetuximab. *J Clin Oncol*. 2008;26(3):374-9.
12. De Roock W, Piessevaux H, De Schutter J, et al. KRAS wild-type state predicts survival and is associated to early radiological response in metastatic colorectal cancer treated with cetuximab. *Ann Oncol*. 2008;19(3):508-15.
13. Di Fiore F, Blanchard F, Charbonnier F, et al. Clinical relevance of KRAS mutation detection in metastatic colorectal cancer treated by cetuximab plus chemotherapy. *Br J Cancer*. 2007;96(8):1166-9.
14. Khambata-Ford S, Garrett CR, Meropol NJ, et al. Expression of epiregulin and amphiregulin and K-ras mutation status predict disease control in metastatic colorectal cancer patients treated with cetuximab. *J Clin Oncol*. 2007;25(22):3230-7.
15. Amado RG, Wolf M, Peeters M, et al. Wild-type KRAS is required for panitumumab efficacy in patients with metastatic colorectal cancer. *J Clin Oncol*. 2008;26(10):1626-34.

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