Cancer Biology & Therapy 14:10, 877–878; October 2013; © 2013 Landes Bioscience

Multi-kinase modulation for colon cancer therapy

Paul Dent

Department of Neurosurgery; Massey Cancer Center; Virginia Commonwealth University; Richmond, VA USA

Keywords: BAY43-9006, RAF inhibitor, cetuximab, colorectal cancer therapy, combined therapy, sorafenib, sorafenib and cetuximab

Submitted: 08/15/13

Accepted: 08/16/13

http://dx.doi.org/10.4161/cbt.26176

Correspondence to: Paul Dent;
Email: pdent@vcu.edu

Commentary to: Al-Marrawi MY, Saroya BS, Brennan MC, Yang Z, Dykes TM, El-Deiry WS. Off-label use of cetuximab plus sorafenib and panitumumab plus regorafenib to personalize therapy for a patient with V600E BRAF-mutant metastatic colon cancer. Cancer Biol Ther 2013; 14:703-10; PMID:23792568; http://dx.doi.org/10.4161/cbt.25191

It is now well recognized that in the vast majority of tumor types, for the approach of "kinase inhibition" to exhibit a significant effect, whether the data are from an in vitro assay, an animal model or the clinic, requires that multiple complementary kinases be simultaneously inhibited. This combined inhibition is not only kill the tumor cell but also to suppress and kill tumor cells that seek to avoid the initial induction of death processes via compensatory survival signaling mechanisms.[1] Even within the broad brush definition of carcinomas from a particular organ, there are a range of mutations which present that will profoundly or sometimes more subtly change the paradigm for therapeutic intervention using multiple kinase inhibitor combinations. For example, in colorectal cancer the K-RAS oncogene frequently has an activating mutation implying that inhibition of RAF-MEK1/2-ERK1/2 signaling, but not an initiating receptor upstream of K-RAS, could have a therapeutic effect; however, some colon cell lines with the K-RAS mutation are still noted to be sensitive to upstream ERBB1 inhibitors.[2,3] Also, compensatory feedback survival signaling loops can cause, after inhibition of a mutant active intracellular oncogenic kinase such as B-RAF V600E, a survival activation of growth factor receptors in a tumor cell.[4] The clinical studies in the manuscript by Al-Marrawi et al. describe the rational combination of signaling inhibitors in a colon cancer patient whose tumor cells express a mutant active B-RAF V600E protein that signals into the MEK1/2-ERK1/2 pathway downstream of K-RAS; this is a particularly aggressive form of colon cancer for which few rational therapeutic interventions have been available until recent times.[5,6]

The patient presented with metastatic disease (stage IV) and received FOLFOX with bevacizumab as standard of care treatment, however they exhibited disease progression on this regimen. Genetic analysis revealed that these colon tumors expressed the mutant activated form of B-RAF, V600E. The patient was offered off-label sorafenib (to inhibit B-RAF V600E) and cetuximab (to inhibit ERBB1 signaling). The patient exhibited a mixed response with some tumors continuing to grow but with resolution of other nodules. The patient remained on this regimen for 7 mo with an excellent performance status, exceeding the expected survival of a patient expressing B-RAF V600E colon cancer. After 7 mo the patient's therapy was switched from sorafenib to single agent regorafenib; regorafenib is an analog of sorafenib that was approved by the FDA in September 2012. Finally the patient's therapy became regorafenib combined with another anti-ERBB1 antibody panitumumab, and has been on this therapy for >4 mo with stable disease. All of the individual and drug combinations were well tolerated in this patient.

Sorafenib has been combined with multiple cytotoxic therapies in the clinic with multiple on-going Phase I/II/II trials, and at present there is an open Phase I trial combining sorafenib and cetuximab (NCT 00326495).[7] In another recent Phase I trial, sorafenib was combined with the ERBB1/ERBB2 inhibitor lapatinib, with several significant partial responses and multiple patients with stable disease.[8] At the most recent ASCO meeting there

was a plenary presentation on the use of dabrafenib plus trametinib in patients with BRAF-mutant colon cancer, i.e., a sorafenib-like drug combined with a MEK1/2 inhibitor. Approximately 40 patients were treated with this off-label combination, the individual agents having been approved by the FDA on 29 May 2013 as options for B-RAF mutant melanoma. The reported results in B-RAF mutant colon cancer were promising with one complete response and several partial responders. Thus at this point in time such a combination therapy becomes a reasonable option for this patient should their disease progress. Collectively, the findings of the present manuscript and those of other trials tend to argue that combined inhibition of RAF pathway signaling with inhibition of ERBB receptor signaling may be a promising approach to treat cancer.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Acknowledgments

PD is funded by R01 DK52825.

References

1. Dent P, Curiel DT, Fisher PB, Grant S. Synergistic combinations of signaling pathway inhibitors: mechanisms for improved cancer therapy. Drug Resist Updat 2009; 12:65-73; PMID:19395305; http://dx.doi.org/10.1016/j.drup.2009.03.001
2. Carón RW, Yacoub A, Li M, Zhu X, Mitchell C, Hong Y, Hawkins W, Sasazuki T, Shirasawa S, Kozikowski AP, et al. Activated forms of H-RAS and K-RAS differentially regulate membrane association of PI3K, PDK-1, and AKT and the effect of therapeutic kinase inhibitors on cell survival. Mol Cancer Ther 2005; 4:257-70; PMID:15713897
3. Carón RW, Yacoub A, Zhu X, Mitchell C, Han SI, Sasazuki T, Shirasawa S, Hagan MP, Grant S, Dent PH-RAS. H-RAS V12-induced radioresistance in HCT116 colon carcinoma cells is heregulin dependent. Mol Cancer Ther 2005; 4:243-55; PMID:15713896
4. Prahallad A, Sun C, Huang S, Di Nicolantonio F, Salazar R, Zecchin D, Beijersbergen RL, Bardelli A, Bernards R. Unresponsiveness of colon cancer to BRAF(V600E) inhibition through feedback activation of EGFR. Nature 2012; 483:100-3; PMID:22281684; http://dx.doi.org/10.1038/nature10868
5. Roth AD, Tejpar S, Delorenzi M, Yan P, Fiocca R, Klingbiel D, Dietrich D, Biesmans B, Bodoky G, Barone C, et al. Prognostic role of KRAS and BRAF in stage II and III resected colon cancer: results of the translational study on the PETACC-3, EORTC 40993, SAKK 60-00 trial. J Clin Oncol 2010; 28:466-74; PMID:20008640; http://dx.doi.org/10.1200/JCO.2009.23.3452
6. Al-Marrawi MY, Saroya BS, Brennan MC, Yang Z, Dykes TM, El-Deiry WS. Off-label use of cetuximab plus sorafenib and panitumumab plus regorafenib to personalize therapy for a patient with V600E BRAF-mutant metastatic colon cancer. Cancer Biol Ther 2013; 14; PMID:23792568
7. BAY 43-9006 Plus Cetuximab to Treat Colorectal Cancer. Identifier: NCT00326495. Available online at http://clinicaltrials.gov/ct2/show/NCT00326495?
8. Simonelli M, Zucali PA, Lorenzi E, Rubino L, De Vincenzo F, De Sanctis R, Perrino M, Mancini L, Di Tommaso L, Rimassa L, et al. Phase I pharmacokinetic and pharmacodynamic study of lapatinib in combination with sorafenib in patients with advanced refractory solid tumors. Eur J Cancer 2013; 49:989-98; PMID:23146956; http://dx.doi.org/10.1016/j.ejca.2012.10.016