Colorectal cancer is the second most common cause of cancer death in the United States. In the last two decades, advances in the treatment of these cancers have led to a clinically meaningful improvement in overall survival for patients with both metastatic and localized disease. However, progress in treatment has relied primarily on the development of refined combinations of empiric cytotoxic chemotherapy and has largely not been driven by insights into the molecular or genetic features of colorectal cancer. Today, the primary biologic agents used in colorectal cancer therapy are the anti-EGFR antibodies cetuximab and panitumumab and the VEGFA-directed antibody bevacizumab, both given in combination with cytotoxic chemotherapy. Although cetuximab is directed against the EGFR oncoprotein, this use in the second-line setting is guided by the absence of RAS alterations rather than any positive biomarker. Indeed, despite the wealth of molecular research on this disease, there are currently no targeted therapies in colorectal cancer guided by a positive predictive biomarker.

In 2012, The Cancer Genome Atlas (TCGA) Network published the most comprehensive systematic molecular characterization of colorectal cancer to date, revealing genomic amplifications or mutations of the tyrosine kinase–encoding gene ERBB2 (also known as HER2) in 7% of colorectal tumors, suggesting a novel potential therapeutic target for this cancer (1). In both breast and gastrointestinal adenocarcinomas, patients with ERBB2 amplification are routinely treated with a combination of the ERBB2-directed antibody trastuzumab and chemotherapy. However, the ERBB2 findings of the TCGA colorectal cancer study have not been translated into changes in clinical practice. In this issue of Cancer Discovery, Kavuri and colleagues (2) report on the functional significance of ERBB2 somatic mutations in colorectal cancer. Introduction of the ERBB2 mutations S310F, L755S, V777L, V842I, and L866M into immortalized mouse colon epithelial cells led to activation of downstream signaling pathways and promoted anchorage-independent cell growth, confirming their transforming capacity, similar to results when many of these mutations were also evaluated in nontransformed breast epithelial MCF10A cells (3). Further experiments in this report also address two specific clinical scenarios where the presence of ERBB2 mutations may have relevance in guiding therapy: the potential for these mutations to serve as a negative marker for anti-EGFR therapy and, more significant, the potential of these alterations to identify patients who would benefit from ERBB2-directed therapy.

Although the most common known marker of intrinsic resistance to anti-EGFR therapy in colorectal cancer is the presence of KRAS mutations, there are a substantial number of patients with KRAS (or NRAS) wild-type tumors who fail to respond to EGFR antibodies. As the antibodies used in colorectal cancer do not inhibit ERBB2, a sibling of EGFR, the presence of somatic alterations leading to enhanced ERBB2 activity may serve as an additional negative predictor for these antibodies. Previous studies demonstrated that ERBB2 amplification confers resistance to cetuximab in preclinical models (4, 5). Furthermore, these studies suggested an association between ERBB2 amplification and clinical resistance to cetuximab. However, this latter analysis was limited by the small number of patients. Kavuri and colleagues present new data suggesting that ERBB2 mutations may serve as a novel mechanism of resistance to EGFR antibodies, cetuximab and panitumumab, both in vitro and in vivo, including in patient-derived xenograft (PDX) models. The totality of these results, when coupled to our understanding of the activity of these signaling pathways, suggests that the presence of ERBB2 somatic alterations may serve as another mediator of resistance to EGFR-targeted therapy in RAS wild-type colorectal cancer. This question should be evaluated further in large clinical cohorts, to determine if we could use ERBB2 status to spare additional patients the costs and toxicity of EGFR-directed therapy if there is no reasonable anticipation of benefit. Besides their role as negative predictors of response to EGFR antibodies, the discovery of recurrent ERBB2 mutations and amplifications provides an exciting opportunity to develop treatment strategies directly targeting genomic alterations in colorectal cancer. Kavuri and colleagues evaluate the effect of ERBB2-directed therapy in ERBB2-mutated colorectal cancer in vitro and in vivo. They first demonstrate that engineered intestinal cell lines harboring ERBB2 mutations are highly sensitive to the irreversible EGFR/ERBB2 tyrosine kinase inhibitors neratinib and afatinib, with these inhibitors
inducing effective inhibition of ERBB2 and its downstream pathways. In addition, xenografts from these cell lines were also sensitive to both neratinib and the combination of neratinib and trastuzumab. In contrast, single-agent neratinib in a PDX harboring ERBB2 L866M mutation and amplification resulted in tumor stabilization, whereas the combination of trastuzumab and neratinib was required for tumor regression. In another PDX harboring ERBB2 S310Y mutation, single-agent lapatinib or neratinib had a modest effect, slowing tumor growth. Again, the combination of trastuzumab with either lapatinib or neratinib produced tumor regression. Both PDX models were resistant to trastuzumab alone. Histologic examination of the tumors after treatment revealed decreased cell proliferation and phosphorylation of MAPK and S6 in the tyrosine kinase inhibitor monotherapy and combination group, whereas the trastuzumab monotherapy tumors did not show any evidence of decreased proliferation or downstream pathway inhibition.

Irreversible EGFR/ERBB2 inhibitors have also shown efficacy in preclinical models of ERBB2-mutated breast and lung cancers (3, 6), results which have led to clinical trials evaluating neratinib in a variety of solid tumors harboring ERBB2 mutations (Clinicaltrials.gov identifier NCT01953926). Furthermore, based on encouraging preclinical studies in ERBB2-amplified colorectal cancer (4, 5), a phase II clinical trial of dual ERBB2 blockade was conducted and recently presented at the American Society of Clinical Oncology Annual Meeting (7). Patients with ERBB2-amplified, KRAS exon 2 wild-type, metastatic colorectal cancer who progressed after multiple lines of therapy were treated with the combination of trastuzumab and lapatinib. Of 913 patients screened, 44 (4.8%) were found to be treated with the combination of trastuzumab and lapatinib. Of 764 patients treated in the combination group, whereas the trastuzumab monotherapy group, whereas the trastuzumab monotherapy tumors did not show any evidence of decreased proliferation or downstream pathway inhibition.

In conclusion, several lines of preclinical data are now converging to suggest that ERBB2 activating mutations or amplifications may be new biomarkers that predict resistance to anti-EGFR therapy. More importantly, when these events occur in the absence of KRAS mutations, there is increasing enthusiasm that ERBB2 may represent a new target for biomarker-driven therapy in a subset of colorectal cancer patients. Although in vitro studies have demonstrated the potential for small-molecule kinase inhibitor sensitivity in these patients, the clinical importance of the clinical data in ERBB2-amplified colorectal cancer and the preclinical studies in this issue, combinations of small-molecule and antibody inhibitors may have the greatest potential.

Key questions remain about the genomic context in which somatic ERBB2 alterations occur in colorectal cancer. In the original TCGA study, the ERBB2 alterations were largely in the microsatellite-stable (MSI) population. In the TCGA study, the ERBB2 mutations seen in patients with microsatellite-unstable (MSI) hypermutated cancers did not fall at the sites of hotspot codons where mutations are established to be activating. Indeed, Kavuri and colleagues’ study in this issue focuses on the MSS population. More recently, however, ERBB2 mutations at such hotspot loci were reported to be recurrent in MSI colorectal cancer. Kloth and colleagues (8) reported that 15% of BRAF wild-type MSI colorectal cancers harbor ERBB2 mutations, with these tumors harboring highly recurrent L755S and V842I substitutions, as well as the new variants L726F, A848T, and G865R. In that study, MSI colorectal cancer cell lines harboring such ERBB2 mutations were highly sensitive to irreversible EGFR/ERBB2 small-molecule tyrosine kinase inhibitors, highlighting their potential role in the treatment of ERBB2-mutated colorectal cancers regardless of mismatch repair status.

An additional and highly clinically and mechanistically relevant observation regarding the role of somatic ERBB2 alterations in colorectal cancer relates to the lack of exclusivity of these events with canonical KRAS mutations. Kavuri and colleagues’ study summarized previously sequenced colorectal cancer tumors with ERBB2 mutation, finding that half (6 of 12) had a co-occurring KRAS mutation. Notably, KRAS mutations were observed in tumors harboring specific ERBB2 codon mutations that are both found recurrently in this disease and also functionally demonstrating to be activating, such as the V842I alteration. Similarly, Kloth and colleagues reported that three of 14 of ERBB2-mutated MSI colorectal cancers also harbored KRAS mutation. Although this co-occurrence could be expected in hypermutated MSI tumors, it is a surprising finding in the nonhypermutated tumors. Whether these coexisting alterations reflect intratumor heterogeneity or if, indeed, individual tumor cells harbor both such events is unknown. Most notably, the functional studies to date have exclusively evaluated mutant or amplified ERBB2 as a target in tumors or models lacking such KRAS alterations. Further studies will be needed to address both the etiology of this co-occurrence and the functional implications. However, even in the case of intratumor heterogeneity, the presence of KRAS mutations can readily be predicted to have implications for the treatment of these cancers, as they may confer resistance to ERBB2-directed therapies that are showing initial promise in the KRAS wild-type setting.

Disclosure of Potential Conflicts of Interest

A.J. Bass is a consultant/advisory board member for Strand Life Sciences. No potential conflicts of interest were disclosed by the other author.

Grant Support

A.J. Bass is supported by a Research Scholar Award from the American Cancer Society and from the NCI (P01CA098101).

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