PIK3CA exon 20 mutations as a potential biomarker for resistance to anti-EGFR monoclonal antibodies in KRAS wild-type metastatic colorectal cancer: a systematic review and meta-analysis

C. Mao1, Z. Y. Yang1, X. F. Hu1, Q. Chen2 & J. L. Tang1*

1Division of Epidemiology, School of Public Health and Primary Care, the Chinese University of Hong Kong, Hong Kong; 2Department of Epidemiology, School of Public Health and Tropical Medicine, Southern Medical University, Guangzhou, People’s Republic of China

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Background: We conducted a systematic review and meta-analysis to dissect the association between PIK3CA mutations and resistance to anti-epidermal growth factor receptor (EGFR) monoclonal antibodies (MoAbs) according to PIK3CA exon of mutations in metastatic colorectal cancer (mCRC).

Methods: We systematically identified studies exploring the association between PIK3CA mutations and clinical outcomes of mCRC patients treated with anti-EGFR MoAbs. The primary clinical outcomes included objective response rate (ORR), progression-free survival (PFS), and overall survival (OS). The pooled relative risk (RR) or hazard ratio (HR) was estimated by using fixed effect model or random effect model according to heterogeneity between studies.

Results: Thirteen studies were considered eligible, with 576 mCRC patients included. In KRAS wild-type mCRC patients, we observed a lower ORR in patients with PIK3CA exon 20 mutations [3 studies, 377 patients; ORR = 37% versus 3%; RR = 0.25; 95% confidence interval (CI) 0.05–1.19; P = 0.082], although the result was not statistically significant because of the small sample size. Only one study provided survival data according to the PIK3CA exon of the mutations, in which PIK3CA exon 20 mutations were statistically significantly associated with shorter PFS (HR = 2.52; 95% CI 1.33–4.78; P = 0.013) and OS (HR = 3.29; 95% CI 1.60–6.74; P = 0.006) in KRAS wild-type mCRC patients treated with anti-EGFR MoAbs. The predictive power of exon 20 mutation is greater than exon 9 mutations and all exons mutations in terms of ORR, PFS, and OS.

Conclusion: These analyses suggest that PIK3CA exon 20 mutations may be a potential biomarker for resistance to anti-EGFR MoAbs in KRAS wild-type mCRC.

Key words: colorectal cancer, meta-analysis, monoclonal antibodies, PIK3CA

introduction

Colorectal cancer (CRC) is one of the commonest human malignant diseases and a leading cause of cancer-related deaths worldwide. Despite recent advances in chemotherapy, the 5-year survival rate for metastatic colorectal cancer (mCRC) remains below 10% [1]. Recently, two monoclonal antibodies (MoAbs) targeted at epidermal growth factor receptor (EGFR), the chimeric immunoglobulin G1 MoAb cetuximab and the fully humanized immunoglobulin G2 panitumumab, were found effective in combination with chemotherapy or as single therapeutic agent for chemotherapy-resistant mCRC [2, 3]. However, only 10%–20% of mCRC patients are responsive to the new treatments [4]. It is important to identify those who are more likely to respond and make the treatment more personalized.

It has been reported that oncogenic activation of intracellular signaling pathways downstream of EGFR, including the RAS-RAF-MAPK and PI3K-PTEN-AKT signaling pathways, are important mechanisms for generating resistance to anti-EGFR MoAbs. Active KRAS mutations, in the RAS-RAF-MAPK pathway, have been shown to be a major predictive marker of resistance to anti-EGFR MoAbs [5–7]. However, KRAS mutations only account for ~30% to 40% of nonresponsive patients [8–12]. It has yet to be explained why a large number of patients with wild-type KRAS tumors do not respond to the treatment. In 2005, active PIK3CA (phosphoinositide-3-kinase, catalytic, alpha polypeptide) mutations, in the PI3K-PTEN-AKT pathway, were found likely to be able to predict resistance to anti-EGFR MoAbs in unselected mCRC patients and more importantly in wild-type KRAS patients whose nonresponse to the treatment cannot be predicted by KRAS mutations [13].
PIK3CA mutations are observed in some 10%–18% of CRC patients, mainly occurred in exon 9 (E542K, E545K) and exon 20 (H1047R) [13, 14]. The PIK3CA gene encodes the p110α protein, which is a catalytic subunit of the class I PI3K. PIK3CA mutations lead to constitutive activation of p110α enzymatic activity, stimulate AKT signaling, and allow growth-factor-independent growth. It has been reported that PIK3CA mutation had a negative impact on the prognosis of a variety of human tumors such as breast cancer and mCRC. In mCRC, several studies have evaluated the role of PIK3CA mutations in predicting resistance to anti-EGFR MoAbs [13–25]. The results are however highly inconsistent and remain uncertain whether, when, and to what extent PIK3CA mutations could affect responsiveness of mCRC patients to anti-EGFR MoAbs. For example, Moroni et al. [13] in 2005 showed that the relative rate in objective response to the treatment between PIK3CA mutant and wild-type patients was 1.04, while in 2010, De Roock et al. [21] reported a relative rate of 0.56. Is this difference merely a result of chance or methodological heterogeneity or are the studies bound to differ? We thus conducted this systematic review to dissect the associations between PIK3CA mutations and prognosis of mCRC patients in relation to anti-EGFR MoAbs. We also proposed criteria for factors that can predict resistance to a treatment and a framework that can systematically explain the heterogeneity in current studies and guide future studies and treatment.

methods

literature search

Comprehensive computerized literature search of PubMed, EMBASE, Chinese Biomedical Database (CBM), and Wan Fang Digital Journals until 30 December 2010 was carried out. Following three groups of search terms were used to identify relevant studies: metastatic colorectal cancer (e.g. ‘metastatic colon cancer’, ‘metastatic rectal cancer’, ‘mCRC’), PIK3CA (e.g. ‘phosphoinositide-3-kinase catalytic, alpha polypeptide’, ‘PI 3-kinases, catalytic, alpha polypeptide’, ‘PI3KCA’), and clinical outcomes (e.g. ‘objective response’, ‘progression-free survival’, ‘overall survival’). All eligible studies were retrieved and their bibliographies were scrutinized for further relevant publications. Figure 1 is the flow chart of literature search and study selection and results in each step.

inclusion criteria

Studies meeting all the following two inclusion criteria were eligible and included in the review: (i) those exploring the relation between PIK3CA mutations and clinical outcomes of mCRC patients treated with anti-EGFR MoAbs; (ii) those using one or more of the following as outcomes to assess tumor response and prognosis: objective response, progression-free survival (PFS), and overall survival (OS).

data extraction

Data extraction was carried out independently by two reviewers. Disagreements were resolved by discussion between the two. If these two reviewers could not reach a consensus, a third reviewer was consulted to resolve the dispute and a final decision was made by the majority of the votes. The following data were collected from each study: first author’s name, year of publication, study design, total number of patients included in the study, number of patients by PIK3CA mutation status, line of treatment, study treatment protocols, response criteria, objective response rate (ORR), PFS, and OS. The clinical end points were extracted separately according to KRAS mutation status if possible as well as PIK3CA mutation status.

framework of analysis

As KRAS mutation is already shown to be a clear indicator of nonresponse to the treatment of anti-EGFR MoAbs, the value of PIK3CA mutation in predicting nonresponsive patients would largely remain in patients with wild-type KRAS. This is to say that the relation between PIK3CA mutation and prognosis in KRAS mutant patients who barely respond to the treatment, such as the RR(KRASmut) in Figure 2, would be close to 1 unless there are more complicated interactions between KRAS and PIK3CA mutations. Thus, the primary analyses of interest should be to estimate the relation between PIK3CA mutation and prognosis in wild-type KRAS patients, such as the RR(KRASwild) in Figure 2. Any analyses including patients with KRAS mutation or those unselected by, or of unknown KRAS status, are thus redundant and will considerably underestimate the power of PIK3CA mutation for predicting nonresponse as almost all KRAS mutant patients are nonresponders and PIK3CA mutation will not add any discriminating power. The framework can therefore be used to explain the heterogeneity in studies of patients with different KRAS mutation status. The predictive power of PIK3CA is expected to be the highest in KRAS wild-type patients, intermediate in those with unknown KRAS status, and lowest in KRAS mutant patients.

statistical methods

The primary end points were objective response, PFS, and OS. The association between PIK3CA mutations and ORR was expressed as a relative risk (RR), namely the overall response rate in PIK3CA mutant patients divided by that in PIK3CA wild-type patients. The association between PIK3CA mutations and PFS or OS was expressed as a hazard ratio (HR).

Heterogeneity was assessed by the Q-test with a df equal to the number of included studies minus one [26]. A P-value >0.10 for the Q-test suggests that the variation in the result may have resulted purely by chance. The pooled RR or HR was estimated by using the fixed effect model unless heterogeneity (i.e. when P ≤ 0.10) was found and cannot be explained [27]. Absence of statistically significant heterogeneity is not the evidence for the
lack of true heterogeneity. As we have explained in the theoretical framework, the RRs in patients with different KRAS mutation status are bound to differ. In order to explain the heterogeneity and dissect the complicated relation between PIK3CA status and prognosis in relation to the treatment, we did stratified analyses and estimated the pooled RR according to KRAS mutation status. As different biological effects have been suggested for PIK3CA exon 9 (helical domain) and exon 20 (kinase domain) mutations [28–30], the RR or HR was also estimated for each type of mutation as well as for any PIK3CA mutations. In the case that heterogeneous results were combined, the random effect model was used [31].

Sensitivity analyses were carried out to check if modification of our inclusion criteria affected the final results. Begg’s funnel plots and Egger’s linear regression test were used to assess the possibility of publication bias [32]. If deemed necessary, the Duval and Tweedie nonparametric ‘trim and fill’ method would be used to estimate the ‘unbiased’ effect [33]. All the statistical analyses used in this study were carried out with RevMan 5.0 and Stata 10.1 (Stata, College Station, TX).

results

study characteristics

Figure 1 is the flow chart of literature search and study selection. The search in bibliographic databases yielded 367 citations, of which 37 were classified as potentially relevant and subjected to full text assessment. A total of 14 studies met the inclusion criteria [13–25, 34]. One study [34] was excluded because the same data were available in other study, which was already included [19]. Thus, 13 studies were included in the final analyses [13–25]. Table 1 shows the main characteristics of the 13 studies for patients treated with anti-EGFR MoAbs, all of which were retrospective cohort studies. Six studies [13, 17, 18, 21, 22, 25] provided data in KRAS wild-type patients and eight [13–19, 22] were in patients unselected by KRAS mutation status. In KRAS wild-type patients, four studies [13, 17, 21, 22] examined exon 9 mutation and three examined exon 20 mutations. In patients unselected by KRAS mutation status, six studies [13, 14, 16–18, 22] examined exon 9 and three [13, 17, 18] examined exon 20. Five studies [15, 17, 18, 21, 22] were carried out in chemorefractory mCRC patients and eight [13, 14, 16, 19, 20, 23–25] studies in patients with chemorefractory or chemonaive mCRC patients. Anti-EGFR MoAb was given as first-line treatment in 1 study [23] and as first-line or subsequent lines in 12 studies [13–22, 24, 25]. Patients received anti-EGFR MoAb monotherapy in two studies [15, 16] and anti-EGFR MoAb-based therapy in the remaining studies [13, 14, 17–25].

PIK3CA mutations and ORR in KRAS wild-type patients

Figure 3 is the forest plot of the analysis on the relative risk according to the exon of the mutation in KRAS wild-type patients. In those with mutation on exon 20, the relative risk of objective response in PIK3CA mutant patients relative to PIK3CA wild-type patients is 0.25 [95% confidence interval (CI) 0.05–1.19; \( P = 0.082 \)]. The result suggests that patients with exon 20 mutations have a poorer prognosis in terms of objective response than PIK3CA wild-type patients, although it is not statistically significant partly due to the small sample size. The RR for exon 9 mutation is 0.79 (95% CI 0.45–1.41; \( P = 0.434 \)). With the increased power, the RR for any PIK3CA mutations is 0.59 (95% CI 0.36–0.96) and statistically significant (\( P = 0.034 \)). The predictive power of exon 20 mutation is not statistically significantly greater than that of exon 9 mutation (\( P = 0.170 \)).

PIK3CA mutations and ORR in patients unselected by KRAS mutation status

As we explained in our analysis framework in Figure 2, the RR for PIK3CA mutations in patients unselected by KRAS mutation status is, as expected, closer to 1, in all the three groups than those in KRAS wild-type patients (Figure 4), implying a smaller predictive power. It is 0.60 (95% CI 0.14–2.63) in those with exon 20 mutations, 1.03 (95% CI 0.56–1.89) in those with exon 9 mutations, and 0.75 (95% CI 0.44–1.28) in those with any PIK3CA mutations. Different from what is observed in KRAS wild-type patients, exon 9 mutations do not seem to predict the response in patients unselected by KRAS mutation status, which could be a result of dilution bias or raises a concern about the predictive value of exon 9 mutations.
**Table 1.** Main characteristics of 13 retrospective cohort studies in patients treated with anti-EGFR MoAbs

<table>
<thead>
<tr>
<th>First author</th>
<th>Year of publication</th>
<th>No. of patients assessed</th>
<th>Mutation analysis methods</th>
<th>No. of PIK3CA mutant patients (%)</th>
<th>Line of treatment</th>
<th>Treatment protocols</th>
<th>Response criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moroni [13]</td>
<td>2005</td>
<td>31</td>
<td>DS</td>
<td>3 (9.7)</td>
<td>≥1</td>
<td>C alone, P alone, or C + I based</td>
<td>RECIST</td>
</tr>
<tr>
<td>Lièvre [14]</td>
<td>2006</td>
<td>30</td>
<td>DS</td>
<td>2 (6.7)</td>
<td>≥1</td>
<td>C alone, C + I, or C + FOLFIRI</td>
<td>RECIST</td>
</tr>
<tr>
<td>Cappuzzo [15]</td>
<td>2008</td>
<td>79</td>
<td>Survey or analysis</td>
<td>14 (17.7)</td>
<td>&gt;1</td>
<td>C alone</td>
<td>RECIST or WHO</td>
</tr>
<tr>
<td>Freeman [16]</td>
<td>2008</td>
<td>62</td>
<td>DS</td>
<td>2 (3.2)</td>
<td>≥1</td>
<td>P alone</td>
<td>RECIST</td>
</tr>
<tr>
<td>Perrone [17]</td>
<td>2009</td>
<td>31</td>
<td>DS</td>
<td>4 (12.9)</td>
<td>&gt;1</td>
<td>C + I</td>
<td>RECIST</td>
</tr>
<tr>
<td>Prenen [18]</td>
<td>2009</td>
<td>200</td>
<td>AD + DS</td>
<td>23 (11.5)</td>
<td>&gt;1</td>
<td>C alone or C + I</td>
<td>RECIST</td>
</tr>
<tr>
<td>Sartore-Bianchi [19]</td>
<td>2009</td>
<td>110</td>
<td>DS</td>
<td>15 (13.6)</td>
<td>≥1</td>
<td>C alone, P alone, or C + I based</td>
<td>RECIST</td>
</tr>
<tr>
<td>Souglakos [20]</td>
<td>2010</td>
<td>168</td>
<td>Sanger sequencing</td>
<td>26 (15.5)</td>
<td>≥1</td>
<td>C + Chem</td>
<td>RECIST or WHO</td>
</tr>
<tr>
<td>De Roock [21]</td>
<td>2010</td>
<td>743</td>
<td>DxS</td>
<td>108 (14.5)</td>
<td>&gt;1</td>
<td>C + Chem</td>
<td>RECIST</td>
</tr>
<tr>
<td>Perkins [22]</td>
<td>2010</td>
<td>42</td>
<td>DS</td>
<td>6 (14.3)</td>
<td>&gt;1</td>
<td>C alone, P alone, or C + I, or C + FOLFIRI</td>
<td>RECIST</td>
</tr>
<tr>
<td>Tol [23]</td>
<td>2010</td>
<td>436</td>
<td>DS</td>
<td>43 (9.9)</td>
<td>1</td>
<td>C + capcitabine + oxaliplatin + bevacizumab</td>
<td>RECIST</td>
</tr>
<tr>
<td>Saridaki [24]</td>
<td>2011</td>
<td>112</td>
<td>Sanger sequencing</td>
<td>11 (9.8)</td>
<td>&gt;1</td>
<td>C + I based, or C + oxaliplatin based</td>
<td>NR</td>
</tr>
<tr>
<td>Wong [25]</td>
<td>2011</td>
<td>29</td>
<td>DxS</td>
<td>3 (10.3)</td>
<td>≥1</td>
<td>C + capcitabine + oxaliplatin + bevacizumab</td>
<td>RECIST</td>
</tr>
</tbody>
</table>

AD, allelic discrimination; C, cetuximab; Chem, chemotherapy; DS, direct sequencing; DxS, DxS PI3K Mutation Test Kit; EGFR, epidermal growth factor receptor; FOLFIRI, fluorouracil, folinic acid, and irinotecan; I, irinotecan; MoAbs, monoclonal antibodies; NR, not reported; P, panitumumab; WHO, World Health Organization criteria.

### PIK3CA mutations and ORR in chemorefractory patients

As the MoAb treatment is generally recommended only to chemorefractory patients, it is particularly important to know how well PIK3CA mutations can predict prognosis in chemorefractory patients. The RR for exon 20 mutations, exon 9 mutations, and any PIK3CA mutations (Table 2) was very similar to those in Figure 3 for KRAS wild-type patients and to those in Figure 4 for patients unselected by KRAS mutations status. This suggests that either the number of studies is too small to detect any difference or that the PIK3CA mutation and prognosis association is similar in chemorefractory and chemonaive patients.

### PIK3CA mutations and survival

Data for PIK3CA mutations and (PFS and OS) survival in mCRC patients treated with anti-EGFR MoAbs were reported in six studies [15, 18, 20, 21, 23, 24]. A study could report the result in both wild-type patients and patients unselected by KRAS mutation status. Due to different ways and the incompleteness of data reporting, the results could not be sensibly combined in a meta-analysis in most situations.

Five studies for KRAS wild-type patients all reported a shorter median PFS [21, 23] or OS [21, 23, 24] in PIK3CA mutant patients than in PIK3CA wild patients, although none of the results was statistically significant. As explained in our analysis framework in Figure 2, the PIK3CA mutation and survival relation in patients unselected by KRAS mutation status would be diluted to different degrees and thus be more heterogeneous. Indeed, one study found a significant shorter median PFS [20] and two studies found insignificant shorter median OS [15, 24] in PIK3CA mutant patients, whereas three studies found insignificant longer median PFS [15, 18] or OS [18].

One study [21] provided survival data according to the PIK3CA exon of the mutations in KRAS wild-type mCRC patients treated with anti-EGFR MoAbs and showed that PIK3CA exon 20 mutations were statistically significantly associated with shorter PFS (HR = 2.52, 95% CI 1.33–4.78, \(P = 0.013\)) and OS (HR = 3.29, 95% CI 1.60–6.74, \(P = 0.006\)). As expected, the predictive power of exon 20 mutation is also greater than that of any exon mutations (PFS: HR = 1.30, 95% CI 0.91–1.86, \(P = 0.170\); OS: HR = 1.41, 95% CI 0.96–2.06, \(P = 0.090\)) and exon 9 mutations (PFS: HR = 1.11, 95% CI 1.72–0.71, \(P = 0.650\); OS: HR = 1.30, 95% CI 0.82–2.05, \(P = 0.280\)).

**sensitivity analysis and publication bias**

Sensitivity analyses were also carried out by excluding two studies examining anti-EGFR MoAbs as a single treatment in any exons.
and exon 9 in Figure 4, and two studies using two response criteria (RECIST and World Health Organization) in any exons, exon 9, and exon 20 in Figure 3, and any exons in Figure 4. They did not alter the original results materially but reduced the statistical power. Relevant results can be made available at request.

The P-value of the Egger’s test for the asymmetry of the funnel plot based on data on all exons in Figure 4 is 0.06, suggesting that there might be a possibility of publication bias, although other possibilities may also exist, such as true heterogeneity and the method of constructing the funnel plot [35].

**discussion**

This systematic review of 13 studies showed that PIK3CA mutations, in particular on exon 20, were likely to be related to the prognosis of KRAS wild-type mCRC patients treated with the anti-EGFR MoAbs, although the relation has not reached statistically the significance level of 0.05. First, with the increased sample size, the overall RR for all PIK3CA mutations is statistically significant, implying that the insignificant result for exon 20 mutations may be due to a small sample size. Second, the predictive power of exon 20 mutation is greater than exon 9 mutations and all exons mutations both in KRAS wild-type patients and in patients unselected by KRAS mutation status, implying that the effect of the mutation is specific and more likely to be real. Third, as expected according to the analysis framework that we proposed, the RRs for PIK3CA mutations in patients unselected by KRAS mutation status are all diluted and thus closer to one for exon 20 mutations, exon 9 mutations, and any PIK3CA mutations than those in KRAS wild-type patients. Fourth, the RR for PIK3CA exon 20 mutations is 0.25. Such a large effect is in general less likely to be purely a result of bias.

Fifth, in vitro studies found that the gain of function induced by PIK3CA exon 20 mutations (coding for the kinase domain) is independent of Ras binding, whereas that of exon 9 mutations (helical domain) requires Ras-GTP interaction [28]. De Roock et al. [21] confirmed in an epidemiological study in human patients that PIK3CA exon 20 mutations were independent of KRAS mutations in mCRC patients but exon 9 mutations were not. These findings suggest that exon 20 and exon 9 mutations may differ in their power of predicting the prognosis of mCRC patients.

Finally, in addition to the findings in overall response, the same relation was also found in survival data. The study by De Roock et al. [21] provided survival data according to the PIK3CA exon of the mutations, in which PIK3CA exon 20 mutations were statistically significantly associated with shorter PFS and OS in KRAS wild-type patients. As expected, the predictive power of exon 20 mutation is also greater than that of any exon mutations and exon 9 mutations.

For future investigation, more studies are needed to compare, with larger sample size, the predictive value of exon 20 mutations and exon 9 mutations in KRAS wild-type patients.
rather than in patients unselected by KRAS mutation status. For example, according to our calculation using PASS software, ~970 KRAS wild-type patients are needed to draw a firm conclusion (significant level 0.05, power 0.90) on the predictive value of exon 20, assuming that the mutation rate for exon 20 is 3.2% (see ‘Results’ section) in KRAS wild-type patients, the ORR for exon 20 wild-type patients is 37% (see ‘Results’ section), and the RR is 0.25 (Figure 3). More studies are also required for the relation of PIK3CA with survival according to the exon of the mutation as survival is more important a clinical outcome for patient care and decision making than general responses. When more primary studies are available, the role of publication bias could be further examined.

Like other biological markers such as KRAS mutations, PIK3CA exon 20 mutations are suggested to be used to identify those who may respond better to chemotherapies. However, based on the current evidence, we cannot conclude that PIK3CA exon 20 mutation could predict response or resistance to the MoAbs treatment because it may have similar predictive power in patients untreated with the MoAbs. In order to answer the

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**Table 2.** Meta-analyses on the association between PIK3CA mutations and objective response in chemorefractory mCRC patients

<table>
<thead>
<tr>
<th>Patient categories by KRAS and PIK3CA mutation status</th>
<th>No. of Studies</th>
<th>Mutant PIK3CA % Responders/total number</th>
<th>Wild-type PIK3CA % Responders/total number</th>
<th>Strength of association</th>
<th>Test for heterogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>RR (95% CI)</td>
<td>RR (95% CI)</td>
<td><strong>Q</strong> value</td>
<td><strong>P</strong> value</td>
</tr>
<tr>
<td>Unselected patients by KRAS mutation status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All exons</td>
<td>4</td>
<td>9/47 (19.1)</td>
<td>62/296 (20.9)</td>
<td>0.95 (0.52 to 1.73)</td>
<td>0.859</td>
</tr>
<tr>
<td>Exon 9</td>
<td>3</td>
<td>5/25 (20.0)</td>
<td>53/239 (22.2)</td>
<td>0.95 (0.45 to 2.00)</td>
<td>0.893</td>
</tr>
<tr>
<td>Exon 20</td>
<td>2</td>
<td>0/4 (0.0)</td>
<td>46/218 (21.1)</td>
<td>0.69 (0.11 to 4.18)</td>
<td>0.682</td>
</tr>
<tr>
<td>Patients with wild-type KRAS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All exons</td>
<td>4</td>
<td>11/53 (20.8)</td>
<td>166/449 (37.0)</td>
<td>0.59 (0.35 to 0.98)</td>
<td>0.043</td>
</tr>
<tr>
<td>Exon 9</td>
<td>3</td>
<td>6/24 (25.0)</td>
<td>134/355 (37.7)</td>
<td>0.70 (0.37 to 1.34)</td>
<td>0.284</td>
</tr>
<tr>
<td>Exon 20</td>
<td>2</td>
<td>0/10 (0.0)</td>
<td>128/346 (37.0)</td>
<td>0.22 (0.03 to 1.46)</td>
<td>0.116</td>
</tr>
</tbody>
</table>

mCRC, metastatic colorectal cancer; RR, relative risk; 95% CI, 95% confidence interval.
question whether PIK3CA mutations can predict prognosis of the anti-EGFR MoAbs treatment, one must investigate the interaction between PIK3CA mutation status and the antibody treatment in affecting the prognosis [36, 37]. This means that the biomarker-prognosis relation in MoAb treated and untreated patients needs to be estimated and compared. In statistical terms, this interaction is best evaluated in a randomized clinical trial with a control group untreated with the antibody and with subgroup analysis of the predictive value by treatment status. Unfortunately, we have not found any study assessed the predictive value of PIK3CA mutations in this way, pointing to an important need for future research in this field.

If PIK3CA mutation is, indeed, a predictor of response to the antibody, how many mCRC patients could truly benefit from examination of PIK3CA mutation status and then being exempted from the unnecessary treatment? It is estimated that 62% of mCRC patients are KRAS wild-type [38], among whom 3.2% would have exon 20 (according to the present review). After excluding those who may still respond to the treatment even if they carry PIK3CA exon 20 mutations (the proportion of these patients is 0%, according to the present review), ∼2% [i.e. 62% × (3.2%–0%)] of all mCRC patients can truly benefit by being exempted from the treatment.

In conclusion, PIK3CA exon 20 mutations may be a potential biomarker for resistance to anti-EGFR MoAbs in KRAS wild-type mCRC. Large randomized clinical trials according to PIK3CA exon of mutations, in particular in KRAS wild-type patients and in patients untreated with the MoAbs, are needed in order to further confirm the relation and clarify its clinical implications.

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disclosure
The authors declare no conflicts of interest.

references