Overcoming Resistance to Anti-EGFR Therapy in Colorectal Cancer

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OVERVIEW

Our understanding of the genetic and nongenetic molecular alterations associated with anti–epidermal growth factor receptor (EGFR) therapy resistance in colorectal cancer (CRC) has markedly expanded in recent years. Mutations in RAS genes (KRAS/NRAS exons 2, 3, or 4) predict a lack of clinical benefit when anti-EGFR monoclonal antibodies (mAbs) are added to chemotherapy. Genetic events in additional nodes of the mitogen-activated protein kinase (MAPK)–phosphoinositide 3-kinase (PI3K) pathways that bypass EGFR signaling, such as BRAF or PIK3CA mutations or KRAS, ERBB2, or MET amplifications, also may confer resistance to cetuximab or panitumumab. Polymorphisms that block antibody binding as a result of EGFR extracellular domain mutations have been reported. Nongenetic mechanisms, including compensatory activation of receptor tyrosine kinases HER3 and MET, together with high expression of the ligands amphiregulin, transforming growth factor alpha heregulin, and hepatocyte growth factor in the tumor microenvironment also are thought to be involved in resistance. In one-third of the samples, more than one genetic event can be found, and nongenetic events most likely coexist with gene alterations. Furthermore, activation of a gene expression signature of epithelial-mesenchymal transition has been associated with reduced cellular dependence on EGFR signaling. Collectively, this body of work provides convincing evidence that the molecular heterogeneity of CRC plays an important role in the context of resistance to anti-EGFR therapy. Herein, we discuss how this knowledge has been translated into drug development strategies to overcome primary and acquired anti-EGFR resistance, with rational combinations of targeted agents in genomically selected populations, second-generation EGFR inhibitors, and other agents expected to boost the immune response at the tumor site.

Colorectal cancer is the third most common cancer type in Western countries, and mortality as a result of CRC has declined progressively in recent decades.1 This can be attributed not only to cancer screening programs but also to the availability of more effective therapies, both for early-stage and advanced disease. Extensive investigations have uncovered several critical genes and pathways relevant to CRC initiation and progression. The knowledge about these driver molecular alterations has already translated into drug development and biomarker discovery, with EGFR being the most noticeable example. The specific genetic background of the tumor largely influences the efficacy of anti-EGFR therapies. Nearly 70% of CRC samples have heterogeneous genetic alterations in genes involved in EGFR signaling, which negatively affect response to the mAbs cetuximab and panitumumab. Furthermore, molecular heterogeneity of CRC has been recognized as pivotal in the evolution of clonal populations during anti-EGFR therapies.2 In this manuscript, we summarize the current understanding about primary (de novo) and secondary (acquired) resistance to anti-EGFR therapies in metastatic CRC (mCRC) and about emerging predictive biomarkers that could ultimately help define the optimal combination therapy for patients in routine clinical practice.

PRIMARY RESISTANCE TO ANTI-EGFR THERAPY IN ADVANCED CRC

Only 10% of patients with chemotherapy-refractory mCRC achieve objective responses to cetuximab or panitumumab as single agents.3,4 In this setting, KRAS mutations in codons 12 and 13 (exon 2) were the first to be causally implicated in primary resistance to anti-EGFR mAbs.5,6 Cetuximab and panitumumab provide similar overall survival benefit in KRAS exon 2 wild-type, chemotherapy-refractory mCRC.7 Furthermore, in the first- or second-line settings, patients whose tumors harbor KRAS exon 2 mutations do not benefit from the addition of anti-EGFR mAbs to chemotherapy, providing compelling evidence of primary resistance.8-11 Because not all patients with KRAS wild-type disease benefit from targeted agents, many groups investigated addi-
tional biomarkers of resistance that could explain the heterogeneity in clinical response. The next step was to evaluate additional oncogenic events in the MAPK pathway. Approximately 20% of CRC samples harbor activating mutations in BRAF (V600E), NRAS (codons 12, 13, 59, 61, 117, and 146 in exons 2, 3, and 4), or rare variants in KRAS (codons 59, 61, 117, and 146 in exons 3 and 4). Retrospective studies indicate that these events could also underlie resistance to single-agent cetuximab or panitumumab in patients with chemotherapy-refractory mCRC. More recently, randomized studies have shown that mutations in KRAS exons 3 and 4 or NRAS exons 2, 3, and 4 can also predict a lack of clinical benefit of anti-EGFR mAbs when given in combination with chemotherapy in the first-line setting. Patients with CRC that is wild type for all RAS mutations (KRAS and NRAS exons 2, 3, and 4) showed higher response rates and overall survival when cetuximab or panitumumab, versus bevacizumab, was combined with standard chemotherapy. The BRAF V600E mutation, conversely, did not predict resistance to first-line anti-EGFR mAbs plus chemotherapy. However, BRAF mutation is a strong marker of poor prognosis in mCRC. Interestingly, in the second-line setting, the addition of panitumumab to irinotecan had a detrimental effect on survival of a mutant population. It is expected that combinations of anti-EGFR mAbs and selective BRAF inhibitors, which have had unprecedented response rates in early clinical trials, may overcome this negative effect.

Molecular alterations in additional nodes of the EGFR pathway also seem to confer primary resistance to targeted therapies. Among them, PIK3CA exon 20 mutations and PTK7 alterations, which frequently coexist with RAS mutations, have been associated with unresponsiveness to anti-EGFR mAbs. Gene expression signatures that correspond to KRAS-, BRAF-, and PIK3CA–activating mutations predict efficacy of anti-EGFR therapy, suggesting that a shared downstream component of these pathways mediates resistance. Moreover, KRAS, ERBB2, and MET amplifications have been shown to bypass EGFR signaling and activate the pathway. The rarity of these gene amplifications and the relatively small sample size of each study preclude assessment of their clinical value as negative predictive biomarkers of response to anti-EGFR mAbs.

Additionally, the extensive crosstalk among the ERBB family of receptors leads to upregulation of parallel pathways after blockade of a particular receptor as a compensatory adaptive mechanism. One potential mechanism of resistance to anti-EGFR therapy in mCRC is related to the ability of EGFR to form heterodimers with HER3, which results in downstream PI3K and MAPK activation. MET signaling also appears to cooperate with the EGFR pathway to promote the growth of CRC cells. Signals produced by either the cancer cells themselves or by stromal fibroblasts, such as hepatocyte growth factor (HGF), activate parallel receptor tyrosine kinase (RTK) pathways that render CRC cells insensitive to anti-EGFR therapy. These pathways may offer primary escape mechanisms, allowing tumors to circumvent one pathway that has been pharmacologically blocked.

Temporal heterogeneity has also been assessed as a potential mechanism of primary resistance to anti-EGFR therapy. However, when considering matched primary and metastatic samples not previously exposed to targeted agents, the mutational statuses of KRAS, NRAS, BRAF, and PIK3CA are highly concordant, exceeding 90%. In fact, the effectiveness of the anti-EGFR mAbs in RAS wild-type CRC has largely been documented in trials that identified genetic mutations in archived diagnostic samples rather than in new biopsies from metastatic lesions. Importantly, mutations in KRAS, NRAS, and BRAF tend to be mutually exclusive at baseline samples.

**Drug Development to Overcome Primary Resistance to Anti-EGFR Therapy**

The first approach to increase the efficacy of anti-EGFR mAbs tested in the clinic was the combination with vascular endothelial growth factor receptor (VEGFR) pathway inhibitors. Despite potential effects on progression-free survival and objective response, cetuximab plus brivanib (a VEGFR multikinase inhibitor) increased toxicity and did not improve overall survival in patients with chemotherapy-refractory, KRAS wild-type mCRC. Similarly, the addition of panitumumab or cetuximab to bevacizumab and oxaliplatin-based chemotherapy in the first-line setting did not improve outcomes in patients with KRAS wild-type disease. These results raise the possibility of a negative interaction (pharma-
cokinetic and/or pharmacodynamic) between the targeted agents as well as an increased risk of toxicity, leading to frequent treatment delays and reduced dose intensity.

Our current knowledge about primary resistance to cetuximab and panitumumab in mCRC, summarized in Fig. 1A, has led to more promising drug development strategies. Quadruple-negative (KRAS/NRAS/BRAF/PIK3CA wild-type) tumors, which represent up to 30% of cases, are more likely to respond. On the basis of preclinical data and early clinical trials, this type of tumor is particularly sensitive to dual-EGFR targeting (ERBB tyrosine kinase inhibitors [TKIs] added to anti-EGFR mAbs), and this strategy is undergoing clinical validation, as shown in Table 1. The important role of compensatory HER3 signaling and PI3K pathway activation in the development of resistance to anti-EGFR mAbs also has been translated into clinical trials. Results of a randomized, phase II trial in chemotherapy-refractory, KRAS wild-type, anti-EGFR-naive mCRC also suggest a role for MET pathway targeting; the combination of an anti-HGF mAb and panitumumab led to higher response rates and a trend for a better outcome in the population with MET-overexpressing tumors. Another strategy to overcome resistance in this setting is to boost the immune response by increasing the numbers of immune cells engaging in antitumor activity. A growing body of preclinical and clinical evidence shows that the immune system contributes substantially to the therapeutic effects of mAbs in vivo. The combination of immune modulators or checkpoint inhibitors with cetuximab is under evaluation as a first-line therapy of KRAS wild-type mCRC.

**SECONDARY RESISTANCE TO ANTI-EGFR THERAPY IN ADVANCED CRC**

The most common molecular mechanisms that drive secondary resistance to anti-EGFR mAbs in mCRC comprise genetic alterations known to confer primary resistance to cetuximab or panitumumab, as illustrated in Fig. 1B. KRAS and NRAS mutations, mostly affecting exons 3 and 4, were found to emerge in a significant proportion of tumor biopsies and circulating tumor DNA (ctDNA) from patients who had acquired resistance to anti-EGFR mAbs. In one-third of patients, multiple genetic events coexisted in the same sample. BRAF and PIK3CA mutations also were found in biopsies of patients who experienced relapse, although all of these mutations were absent in samples from the same patients at the beginning of the treatment. Multiple repeated biopsies revealed that the percentage of mutant alleles increased under drug exposure and became undetectable after drug withdrawal. These findings suggest that a clonal selection process achieved under treatment pressure plays a major role in determining the final clinical outcome. In addition to acquired PI3K and MAPK downstream mutations, ERBB2 or MET gene amplifications also were described as drivers of acquired resistance to anti-EGFR therapy in cell models and patient samples. Likewise, these events in RTKs leading to parallel signaling activation are enriched in post-treatment biopsies compared with primary tissues. Moreover, acquired EGFR extracellular domain mutations (exon 12) that disrupt cetuximab binding but may be permissive for interaction with panitumumab have been identified recurrently in cetuximab-treated mCRC samples with secondary resistance. Of note, by using a highly sensitive sequencing technology, EGFR S492R was found in 16% of patients after cetuximab exposure and in only 1% after treatment with panitumumab. This mechanism is analogous to other secondary genetic alterations in the target oncoprotein that perturb the conformational state of the kinase drug-binding sites and render the receptor insensitive to the drug (e.g., erlotinib/gefitinib and EGFR T790M).

Non genetic mechanisms also have been linked to anti-EGFR resistance in mCRC. In biopsies from patients who experience disease progression while receiving cetuximab or panitumumab therapy, only a fraction of cells carry activating MAPK mutations, which suggests that wild-type cells also can survive the treatment. Preclinical findings point to the conservation of EGFR dependency in tumors that progressed during anti-EGFR therapy, most likely related to adaptive ligand overexpression. Increased secretion of EGFR ligands amphiregulin and transforming growth factor alpha (TGF alpha) by limited KRAS mutant clones has been proposed as a paracrine resistance mechanism to anti-EGFR mAbs in CRC models. In addition, ectopic production of HGF by stromal cells renders CRC cell lines insensitive to...
EGFR blockade. An autocrine loop with the HER3 ligand heregulin also has been associated with acquired resistance to cetuximab. These experiments suggest that the relative expression of growth factor ligands in the tumor microenvironment and that a cross-talk driven by resistant subpopulations can relay redundant survival pathways and impair responsiveness to kinase inhibitors.

**Drug Development to Overcome Secondary Resistance to Anti-EGFR Therapy**

The first strategy to overcome acquired resistance to anti-EGFR mAbs in mCRC tested in the clinic was treatment with an alternative antibody. Panitumumab has minimal benefit in patients with KRAS wild-type mCRC who have experienced progression while receiving cetuximab as prior therapy. Differences in response rates reported in small cohorts may be related to the inclusion of patients without objective disease progression while receiving cetuximab or for whom cetuximab-containing regimens may have been ceased as a result of toxicity in the absence of disease progression. In both circumstances, re-treatment with panitumumab is expected to demonstrate some degree of clinical activity. Recently, with the hypotheses that the effect of pharmacologic treatment represents a selective pressure and that (preexisting) sensitive subclones may emerge after treatment breaks, the idea of re-exposure to anti-EGFR therapies has been revisited. As shown in Table 1, clinical trials are prospectively evaluating rechallenge with anti-EGFR mAbs in the third-line setting after a response to targeted therapies in the first-line setting. To increase the chances of treatment benefit, only patients with KRAS/NRAS/BRAF wild-type disease are being enrolled.

**Table 1. Resistance Mechanisms to Anti-EGFR Therapies and Drug Development Strategies in Advanced CRC**

<table>
<thead>
<tr>
<th>Setting</th>
<th>Mechanism of Resistance</th>
<th>Strategy</th>
<th>Example</th>
<th>Trial</th>
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<tbody>
<tr>
<td><strong>First-Line Anti-EGFR Therapy</strong></td>
<td>Nongenetic</td>
<td>KRAS/ NRAS/ BRAF/ PIK3CA wt</td>
<td>Anti-EGFR mAb + chemotherapy</td>
<td>Panitumumab + FOLFIRI</td>
</tr>
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<td></td>
<td>Compensatory pathway activation</td>
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<tr>
<td></td>
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<td></td>
<td>Progressing in Third-Line Setting</td>
<td>PI3K-mTOR</td>
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<tr>
<td></td>
<td>After Response to Anti-EGFR Therapy in First-Line Setting</td>
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<td>Anti-EGFR mAbs + MET inhibitors</td>
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Abbreviations: EGFR, epidermal growth factor receptor; CRC, colorectal cancer; wt, wild type; mAb, monoclonal antibody; FOLFIRI, fluorouracil, leucovorin, and irinotecan; TKIs, tyrosine kinase inhibitors; PI3K, phosphoinositide kinase-3; mTOR, mammalian target of rapamycin.

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cetuximab in KRAS exon 2 wild-type or with irinotecan-based chemotherapy alone in patients with KRAS exon 2 mutant disease has not shown any improvement in survival outcomes. Another example is Sym004, a combination of two chimeric mAbs targeting nonoverlapping epitopes of the EGFR extracellular domain III designed to induce a much higher degree of receptor degradation. Encouraging results have been observed in the expansion of the phase I trial, with one-third of patients with anti-EGFR–refractory mCRC experiencing significant tumor shrinkage and prolonged disease stabilization. This suggests that the dependency on EGFR ligands remains an oncogenic driver in this setting. Sym004 is under clinical evaluation in a randomized, proof-of-concept, phase II study in patients with RAS wild-type mCRC that is refractory to anti-EGFR mAbs.

Because acquired anti-EGFR resistance may result from compensatory signaling through ERBB receptors, cetuximab was investigated in combination with pertuzumab (an HER2 heterodimerization inhibitor) in patients with cetuximab-resistant KRAS wild-type mCRC (irrespective of ERBB2 amplification). In a phase I trial, this regimen was not tolerated because of overlapping toxicities, but partial responses and disease stabilization were reported in some patients. The results of clinical trials evaluating alternative combinations in genomically selected populations are highly anticipated.

When a genetic mechanism for secondary resistance is identified, promising strategies under investigation include the combination of anti-EGFR mAbs with MEK inhibitors (when RAS mutant clones emerge) or with HER2- or MET-targeted therapy (in the context of acquired receptor amplification). In principle, a parallel RTK pathway may be activated by compensatory ligand overexpression (nongenetic mechanisms), and the efficacy of these combinations may not be restricted to tumors with gene amplifications. Patients who have tumors that show the EGFR S492R mutation at relapse could be offered panitumumab-based therapy (in the setting of resistance to cetuximab), because panitumumab binds to a distinct epitope of the molecule. Indeed, investigators published a case report of a 5-month clinically beneficial response. The novel anti-EGFR mAb Sym004 is active in preclinical models of acquired EGFR extracellular domain mutations.

**RESISTANCE TO ANTI-EGFR THERAPY IN EARLY-STAGE CRC**

The improved survival with anti-EGFR mAbs added to chemotherapy in patients with RAS wild-type mCRC was the basis for exploring the role of targeted therapies in the adjuvant setting. However, two studies with cetuximab added to standard chemotherapy in stage III colon cancer did not show improved survival outcomes. Although the reasons for these negative findings are not known, divergent effects of anti-EGFR therapy in early-stage versus advanced-stage CRC reinforce the theory that micrometastases behave differently than clinically apparent foci of metastatic disease. In one trial (PETACC-8), a subgroup analysis showed that chemotherapy plus cetuximab was only advantageous for high-risk patients who had pT4pN2, which suggests that they resembled patients who have advanced disease. Investigators also have raised the possibility of a negative interaction between the antibody and oxaliplatin. There is limited clinical evidence from a subgroup analysis (study N0147) suggesting that irinotecan could have been a better choice for combination with cetuximab. Another interesting explanation comes from preclinical experiments that show reduced cellular dependence on EGFR signaling when a tumor cell has transitioned to a mesenchymal phenotype, which is known to support invasion and metastatic seeding of carcinomas. In line with this hypothesis is the finding that early-stage CRC tumors with intrinsic mesenchymal signatures have reduced benefits from treatment with anti-EGFR mAbs given at the time of relapse. In preclinical models, mesenchymal CRC cell lines were particularly sensitive to MET inhibitors.

**CONCLUSION**

The elucidation of de novo and acquired resistance mechanisms arising in the setting of targetable tumor dependencies is guiding the development of rational therapeutic strategies. It is likely that a combination of targeted therapies will be necessary to effectively prevent and/or treat drug-resistant cancers. Colorectal tumors that initially respond to and then relapse after anti-EGFR targeted therapy eventually become highly molecularly heterogeneous. The significant overlap of genetic events associated with primary and secondary resistance supports clonal selection linked to tumor heterogeneity as a major determinant of treatment outcome. It also indicates that the same therapies used for acquired resistance—that is, salvage regimens—could be potentially useful in upfront therapy. The ultimate goals are to increase the magnitude and/or duration of clinical response and to delay the emergence of resistance when such combinations are administered as initial therapy. As recently highlighted by Miso et al., the plethora of alterations that emerge at relapse biochemically converge to activate the EGFR/RAS/MAPK pathway (i.e., convergent evolution), which may facilitate drug development strategies in this setting.

Knowledge of the specific genetic mechanisms of drug resistance and the compensatory parallel signaling activation that occurs during anti-EGFR exposure have been fundamental for the study of alternative kinase inhibitors. Examples include combinations of pan-ERBB, MET, or MEK inhibitors with anti-EGFR mAbs, both in first-line and refractory settings, with promising results in early clinical trials. An alternative approach is to develop second-generation inhibitors of the oncoprotein. For a subset of mCRC tumors, this strategy also has been proven efficacious clinically, but the mechanisms underlying the sensitivity, such as sustained EGFR addiction as a result of ligand overexpression or increased ADCC at the tumor site, are still unknown.

Furthermore, because targeted gene analysis does not always explain the mechanism by which CRC becomes resis-
tant to anti-EGFR therapy, we believe that additional research should be directed toward understanding and controlling the evolutionary process in tumors, paying particular attention to gene expression profiling and interactions with the immune system and microenvironment. Incredible technological developments (e.g., cDNA targeted sequencing) and advances in drug design will enable treatments that are precisely targeted to the unique molecular characteristics of an individual’s cancer. However, until comprehensive molecular profiles of individual tumors becomes feasible, it will be challenging to determine the presence of all of these modifiers of therapy efficacy in clinical practice. Finally, for successful drug translation to the adjuvant setting and increase curability of early-stage CRC, it is imperative to understand the micro- and macroenvironments in which targeted agents exert their effects and also to assess the activities of targeted agents with different chemotherapy backbones in preclinical models of early versus late-stage disease.

Disclosures of Potential Conflicts of Interest


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