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KRAS Mutation in Metastatic Colorectal Cancer And Its Impact on the Use of EGFR Inhibitors

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Abstract

As with many malignancies, cytogenetic information has become increasingly important to the diagnosis and proper treatment of colorectal cancer. In particular, several recent studies have confirmed that KRAS is not only one of the most commonly mutated genes in colorectal cancer, but also essential to treatment decision-making. Several key studies have demonstrated that patients with mutant KRAS do not respond to treatment with epidermal growth factor inhibitors. This finding has several implications for clinicians who treat patients with metastatic colorectal cancer. The following monograph includes discussions on the key issues surrounding the integration of recent data on KRAS status into the care of patients with this disease.

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Target Audience: This activity has been designed to meet the educational needs of hematologist/oncologists and the other healthcare professionals involved in the management of patients with metastatic colorectal cancer.

Statement of Need/Program Overview: Several new cytogenetic subgroups have been identified in colorectal cancer, leading to significant changes in practice, in particular pertaining to the use of epidermal growth factor receptor (EGFR) inhibitors. These emerging data may not be fully understood by practicing hematologists/oncologists in the community setting. A Clinical Roundtable Monograph is the ideal vehicle through which community-based physicians can learn about these recent advances.

Educational Objectives

After completing this activity, the participant should be better able to:

1. Describe the importance of new study findings on the treatment of metastatic colorectal cancer (mCRC) as presented during the 2008 annual meeting of the American Society of Clinical Oncology.
2. Explain the effect of KRAS mutation on the results of clinical trials evaluating new treatment options in mCRC.
3. Identify which patients would respond best to newly available treatment options for mCRC, including EGFR inhibitors.
4. Outline future research directions in the treatment of mCRC.

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Recent Findings on the Natural History and Treatment Of Metastatic Colorectal Cancer

Edward Chu, MD

As with many types of cancer, the study of the underlying molecular genetics and biology associated with the development and progression of colorectal cancer has become as integral to treatment advancement as the development of new drugs. It has been known for some time that the RAS family of genes is one of the most prominent in colonic carcinogenesis.¹ Among the 3 members of this family—HRAS, NRAS, and KRAS—KRAS is the most commonly mutated with respect to colorectal cancer. Approximately 35–40% of all colon tumors exhibit KRAS mutations.² KRAS mutations typically involve codons 12, 13, and 61, with codon 12 being the most commonly mutated in this particular disease.

The presence of KRAS mutations in colorectal cancer is important for several reasons. These mutations typically result in the constitutive activation of the Ras/Raf/MAP kinase signaling pathway, which promotes cell growth, proliferation, and increased survival, and leads to the activation of other key tumorigenic effects.² It is also important to note that KRAS mutations appear to follow mutations in the APC gene. Thus, it appears that alterations in KRAS status are integral to colon cancer formation early in the adenoma-carcinoma sequence.

The evidence indicates that KRAS mutations occur early in this sequence, and it is unlikely that there would be a subsequent change in mutation status, even among patients whose disease recurs after successful surgical resection and adjuvant chemotherapy.

The KRAS pathway has generated interest with regard to antibody therapy targeted against the epidermal growth factor receptor (EGFR). This stems from the fact that the KRAS pathway functions downstream of EGFR, and in so doing, mediates and facilitates the EGFR downstream cellular signaling pathway.³ The constitutive activation of KRAS that is characteristic of the colon cancer–associated mutation leads to unchecked tumor growth as well as the development of anti-EGFR therapy resistance, whether antibody- or small-molecule–based. Thus, the presence of mutated KRAS could be considered both a predictive marker for patients who are unlikely to respond to anti-EGFR therapy and a potential prognostic biomarker.

Retrospective Analyses

Based on these preclinical findings, several relatively small retrospective studies have investigated the predictive value of KRAS status in refractory metastatic colorectal cancer treated with cetuximab or panitumumab (both anti-EGFR monoclonal antibodies), either as single agents or in combination with chemotherapy (Table 1).^{4–10} Taken together, these studies indicate that wild-type KRAS is present in up to 60–70% of patients, and mutant KRAS in 30–40%. Most importantly, these studies demonstrate that, among colorectal cancer patients, response to anti-EGFR therapies is strictly limited to those expressing wild-type KRAS. That being said, it is also important to realize that while the presence of wild-type

Table 1. KRAS Status and Response to Cetuximab in Refractory Metastatic Colorectal Cancer

Study	Treatment	N (% wt)	ORR, %*	
			mt	wt
Lièvre et al, 2006	C-mab + CT	30 (57)	0	65
Benvenuti et al, 2007	P-mab or C-mab ± CT	48 (67)	6	31
De Roock et al, 2007	C-mab ± CT	113 (59)	0	40
Capuzzo et al, 2007	C-mab ± CT	81 (60)	6	26
Di Fiore et al, 2007	C-mab + CT	59 (73)	0	28
Khambata-Ford et al, 2007	C-mab	80 (62)	0	10
Lièvre et al, 2008	C-mab ± CT	76 (64)	0	49

* Note that response is confined to KRAS wt.

ORR=overall response rate; P-mab=panitumumab; C-mab=cetuximab; CT=chemotherapy; mt=mutant KRAS; wt=wild-type KRAS.

KRAS is required for anti-EGFR therapy response, not all such patients will definitely respond to this treatment approach.

Importantly, mutant KRAS also appears to be a prognostic biomarker, meaning that it provides insights as to a patient's likely outcome regardless of the selected therapy. Two retrospective studies evaluating anti-EGFR therapy versus best supportive care found that not only did patients with mutant KRAS expression derive no clinical benefit from EGFR inhibitors, but among patients randomized to best supportive care, those with mutant KRAS expression also experienced a worse overall survival compared to those with wild-type KRAS expression.¹¹ These studies highlight the potential role of KRAS as an important predictive biomarker.

Recent Clinical Studies

In follow-up to these retrospective data in the refractory setting, 2 larger phase III randomized studies (CRYSTAL and OPUS) evaluated cetuximab plus chemotherapy in the frontline setting. The results were presented at the 2008 annual meeting of the American Society of Clinical Oncology (ASCO) and provided important insights about this therapeutic approach related specifically to KRAS status.^{12,13}

The CRYSTAL trial, led by Eric Van Cutsem, MD, PhD, initially enrolled approximately 1,200 patients, 540 of whom had tumors that could be analyzed for KRAS status. Consistent with the retrospective data discussed above, approximately 65% of patients expressed wild-type KRAS and 35% expressed mutant KRAS. These previously untreated patients were administered cetuximab plus FOLFIRI (leucovorin, 5-fluorouracil [5-FU], and irinotecan). Patients with wild-type KRAS experienced a statistically significant improvement in median progression-free survival (PFS): 9.9 months versus 8.7 months among patients treated with FOLFIRI alone ($P=.0167$). Of note, the hazard ratio for patients who received the combination was 0.68 among those expressing wild-type KRAS, versus 0.85 for the original intent-to-treat population. Thus, the addition of cetuximab to FOLFIRI chemotherapy led to a 32% improvement in PFS among patients expressing wild-type KRAS. The overall response rate (ORR) was also statistically significantly higher among wild-type KRAS patients who received the combination, versus those who received FOLFIRI alone (59% vs 43%; $P=.0025$).

By contrast, patients in the CRYSTAL study with mutant KRAS did not derive any clinical benefit from the addition of cetuximab to FOLFIRI chemotherapy. Both median PFS ($P=.75$) and ORR ($P=.46$) were nearly identical among mutant KRAS patients receiving the combination and those receiving chemotherapy alone.

The OPUS study, led by Bokemeyer and colleagues, evaluated cetuximab plus FOLFOX4 (leucovorin, 5-FU,

oxaliplatin) versus FOLFOX4 alone.¹³ In the 2007 presentation of this study, data showed a trend toward improvement among patients in the combination arm versus those receiving FOLFOX4 alone: ORR (primary endpoint) was 46% versus 36%, respectively, although the difference was not statistically significant.

The initial presentation of the results of this study in 2007 did not stratify patients by KRAS status. In a subsequent retrospective analysis, presented at the 2008 ASCO annual meeting, the investigators analyzed the impact of KRAS status on response and survival rates among the patients in the study.¹⁴ A total of 233 of the original 340 patients had tumors evaluable for KRAS status, with wild-type versus mutant percentages consistent with earlier findings. Among patients with wild-type KRAS, those who received cetuximab plus chemotherapy experienced an ORR of 61%, which was much higher than the 36% ORR reported for the FOLFOX4-alone arm in the initial study presentation ($P=.01$). Median PFS increased from 7.2 months to 7.7 months in wild-type KRAS patients receiving FOLFOX alone compared with those receiving FOLFOX plus cetuximab ($P=.01$). With a hazard ratio of 0.57, the addition of cetuximab to FOLFOX4 resulted in a 43% reduction in the risk of disease progression among wild-type KRAS patients.

In contrast, patients with mutant KRAS who received cetuximab plus chemotherapy showed no improvement in ORR versus mutant KRAS patients treated with chemotherapy alone. Moreover, the ORR was lower in those treated on the combination arm versus those on the chemotherapy-alone arm (33% vs 49%).

Median PFS showed a similar reduction in clinical efficacy. Patients with mutant KRAS who received cetuximab plus chemotherapy had a median PFS of 5.5 months, versus 8.6 months among those who received chemotherapy alone. Reasons for reduced ORR and PFS in this subgroup are not yet known.

The Dutch Colorectal Cancer Study Group's CAIRO2 study, the results of which were presented at the 2008 ASCO meeting, also evaluated the impact of KRAS on treatment outcomes.¹⁵ In this phase III randomized trial, nearly 740 patients received either capecitabine plus oxaliplatin chemotherapy (CAPEOX) with the addition of bevacizumab, or a combination of CAPEOX, bevacizumab, and cetuximab. The primary endpoint was PFS, and a retrospective analysis was conducted to evaluate clinical efficacy according to KRAS status.

Among patients with wild-type KRAS, the median PFS was virtually the same among patients treated with chemotherapy plus bevacizumab or chemotherapy plus bevacizumab and cetuximab (10.5 months and 10.7 months, respectively). However, among patients with mutant KRAS expression, the median PFS was 12.5 months and

8.6 months, respectively ($P=.043$). The reasons for this reduced clinical efficacy are not known, and further research is required to investigate the potential link between mutant KRAS and cetuximab therapy.

KRAS is the first molecular biomarker for colorectal cancer that can help identify which patients are most likely to derive benefit from anti-EGFR therapy. KRAS testing should now be considered as standard of care, and sensitive assays for such testing are currently being developed. Several diagnostic labs in the United States already perform KRAS testing, and a reimbursement code for this test is available. European clinicians have already integrated KRAS testing into standard diagnostic procedures for colorectal cancer patients.

Future Directions

Clearly, further research is needed to investigate the potential role of other biomarkers that could predict which patients with wild-type KRAS will respond to anti-EGFR therapy. Along these lines, there is a great deal of interest in exploring other biomarkers, such as EGFR gene copy number, tumor expression of the EGFR ligands including epiregulin and amphiregulin, BRAF status, and tumor expression of PTEN. Other potential biomarkers of interest include proteins involved in parallel and/or alternative signaling pathways to the EGFR pathway.

Evidently, identifying patients who are unlikely to benefit from anti-EGFR antibody therapy is as important as identifying those who will benefit. Sparing patients unnecessary toxicity and expense is incredibly important to successful patient management.

In addition, efforts are underway to develop novel therapeutic approaches for colorectal cancer patients with mutated KRAS. One current hypothesis behind preclinical drug development efforts is that when KRAS is mutated, the colon cancer tumor might be “addicted” to that pathway—ie, dependent on the growth factors that activate that pathway—and more susceptible to inhibitor compounds that target Ras, Raf, or other key enzymes or proteins that are downstream of the Ras pathway.

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Metastatic Colorectal Cancer: Integrating Recent Findings Into Patient Care

Axel Grothey, MD

Recent findings regarding the importance of KRAS status in the treatment of patients with metastatic colorectal cancer directly impact patient care. Integrating these findings into clinical practice means understanding colorectal cancer in new ways and shaping treatment options according to these new views.

Colorectal cancer has essentially become 2 distinct entities: that exhibiting mutated KRAS and that exhibiting wild-type KRAS. Furthermore, the salient feature identified thus far about KRAS status is that patients with mutant KRAS do not respond to EGFR inhibitors. Thus, the main priority in terms of integrating this distinction into practice is that patients with mutant KRAS not be treated with EGFR inhibitors. This change should be adopted immediately, without waiting for an FDA-issued change to the package inserts for cetuximab or panitumumab.

EGFR Inhibitors in the Treatment of Metastatic Colorectal Cancer

One of the looming questions in the wake of these new data is how beneficial EGFR inhibitors are in the first-line setting, when the appropriate patient population is selected for treatment. One must remember that although mutant KRAS status excludes patients who will not respond, wild-type status does not guarantee a response.

The recently presented CRYSTAL and OPUS studies provide some guidance about the place for these antibodies in our treatment algorithms. The CRYSTAL study initially enrolled approximately 1,200 patients who were randomized to receive FOLFIRI plus cetuximab or FOLFIRI alone.¹ As Dr. Chu described, the subgroup of patients with wild-type KRAS who received FOLFIRI plus cetuximab experienced a longer PFS compared to the patient population as a whole.² However, the median PFS gain of just over 1 month was certainly not as strong as we would have liked to achieve.

This limited gain may be due to the chemotherapy regimen that was used. By comparison, the OPUS trial compared FOLFOX4 plus cetuximab to FOLFOX4 alone in the first-line treatment of metastatic colorectal cancer.^{3,4} Patients with wild-type KRAS who received the combination regimen experienced a 24% higher response rate compared to the combination arm as a whole (wild-type and mutant KRAS together).

Interestingly, these data support those of the previously reported CALGB 80302 study, which evaluated FOLFOX versus FOLFIRI with or without cetuximab in a phase II setting.⁵ This study found a 20% higher response rate among patients treated with FOLFOX plus cetuximab compared to those treated with FOLFOX alone. By contrast, the response rate among patients treated with FOLFIRI plus cetuximab was only 8% higher than that associated with FOLFIRI alone.

First-line Therapy

Cetuximab is an appropriate choice for the first-line treatment of wild-type KRAS patients who are either symptomatic from their tumor or who require significant tumor shrinkage to allow for potentially curative resection of liver metastases. More specifically, as noted above, FOLFOX rather than FOLFIRI appears to be the current best choice for the chemotherapy regimen to be combined with cetuximab.

In the palliative setting, where the main goal of therapy is a gain in survival time rather than response rate, bevacizumab-containing regimens would be preferable. Importantly, the pivotal study of irinotecan (IFL) with or without bevacizumab found that the efficacy associated with this antibody is independent of KRAS status.⁶ Thus, a common scenario for late-stage colorectal cancer might be treating progressive disease with a bevacizumab-containing regimen, with cetuximab utilized as a second-line option for wild-type KRAS patients, preferably in combination with chemotherapy.

Combination Antibody Therapy

The rationale for combining EGFR and VEGF inhibitors is obvious: these 2 classes of agents work individually, and combining them may target different systems and thereby improve outcomes compared with either agent alone. However, studies show that combining antibodies is more complicated than might have been expected.

In the BOND-2 study, irinotecan-refractory patients who had received varying numbers of prior chemotherapy regimens were treated with bevacizumab plus cetuximab with or without irinotecan.⁷ The triple combination (n=43)

Table 2. CAIRO2: Summary of Efficacy Results

	COB n=368	COB-C n=368	P
Median PFS (mo) (HR; 95% CI)	10.7 (9.7–12.5)	9.6 (8.5–10.7)	.018 (1.21;1.03–1.45)
Median OS (mo) (HR; 95% CI)	20.4 (18.1–26.1)	20.3 (17.9–21.6)	.21 (1.15; 0.93–1.43)
Response rate (CR + PR)	44%	44%	.88
Disease control rate (CR + PR + SD)	83%	81%	.39

Adapted from Punt et al. *J Clin Oncol.* 2008;26. Abstract LBA4011.

CI=confidence interval; COB=capecitabine, oxaliplatin, bevacizumab; COB-C=COB plus cetuximab; CR=complete response; HR=hazard ratio; PFS=progression-free survival; PR=partial response; SD=stable disease.

compared with bevacizumab plus cetuximab alone (n=40) was associated with a longer time to tumor progression (7.3 months vs 4.9 months), higher response rate (37% vs 20%), and a longer overall survival time (14.5 vs 11.4 months). Toxicity observed in patients on the irinotecan-containing arm was similar to what would be expected for the 2 antibodies alone. It is important to note that the positive findings in this study may be due to a selection process that unavoidably takes place as patients proceed from first- to last-line therapy. Although both regimens in this study contained EGFR and VEGF inhibitors and thereby precluded a direct comparison of the benefit of 1 versus 2 antibodies, the study indicated that combining antibodies appeared safe and potentially beneficial.

From these findings, the logical next step was a direct comparison of dual antibody therapy to single antibody therapy in the first-line setting. The first study to evaluate this approach was the so-called PACCE trial, in which previously untreated patients received a bevacizumab-containing regimen with or without panitumumab.^{8,9} More specifically, the phase III portion of this study evaluated bevacizumab/FOLFOX with or without panitumumab, and the randomized phase II portion evaluated bevacizumab/FOLFIRI with or without panitumumab. The results showed no benefit with the addition of panitumumab to either bevacizumab-containing regimen. In fact, patients receiving panitumumab-containing therapy appeared to fare worse, experiencing more dehydration and diarrhea, than those who did not receive this antibody. Moreover, the lack of benefit with the dual-antibody regimen was seen among both wild-type and

Table 3. CAIRO2: Efficacy Results According to KRAS Genotyping (n=501)

	KRAS wild-type n=305 (61%)	KRAS mutated n=196 (39%)	P
COB	152 (50%)	103 (53%)	
COB-C	153 (50%)	93 (47%)	
Median Progression-Free Survival, mo			
COB	10.7	12.5	.92
COB-C	10.5	8.6	.47
P	0.10	.043	
Median Overall Survival, mo			
COB	23.0	24.9	.90
COB-C	22.2	19.1	.52
P	.49	.35	

Adapted from Punt et al. *J Clin Oncol.* 2008;26. Abstract LBA4011.

COB=capecitabine, oxaliplatin, bevacizumab; COB-C = COB plus cetuximab.

mutant KRAS patients. Consequently, upon preliminary review of the data, panitumumab treatment in this study was discontinued.

More recently, in the CAIRO2 trial, combining bevacizumab with cetuximab plus chemotherapy in the first-line setting did not provide additional benefits beyond bevacizumab plus chemotherapy alone (Table 2).¹⁰ Again, these findings were independent of KRAS status.

Importantly, among patients with mutant KRAS, adding cetuximab to bevacizumab plus chemotherapy was associated with a lessened PFS compared with bevacizumab plus chemotherapy alone (Table 3). Therefore, we can safely conclude that in the first-line setting, dual antibody therapy should not be used outside of a clinical trial.

Dual antibody therapy may be reasonable in the salvage therapy setting. However, only patients with wild-type KRAS would benefit from the addition of an EGFR inhibitor such as cetuximab to a bevacizumab-containing regimen.

It is not yet understood why combining EGFR and VEGF inhibitors does not appear to improve efficacy. Most likely, the phenomenon is one of pharmacodynamics, not pharmacokinetics. It may be that activating one pathway, for example the Ras-mediated pathway, leads to a feedback mechanism that is mediated by another pathway—for example, PI3K, AKT, or PTEN—that blocks the pathway that is initially activated. In other words, if the Ras pathway is activated, the AKT pathway might then provide an inhibitory effect on KRAS. This hypothesis could be easily tested in a laboratory setting, and it is hoped that we will have a clearer understanding of the mechanism in the near future.

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Future Research Directions for the Treatment Of Metastatic Colorectal Cancer

Heinz-Josef Lenz, MD

In considering the future of the treatment of metastatic colorectal cancer, it seems likely that patients will no longer be diagnosed and treated based on pathological and clinical staging alone. Rather, molecular classification and staging will be integrated into treatment decision-making, and a host of prognostic factors will be available at the time of diagnosis.

KRAS status, now being incorporated into the decision of when to use EGFR inhibitors, is a prime example of the direction in which this area of medicine is headed. Identifying additional molecular markers and characteristics on which to base treatment choices in the first, second, or third line of therapy is the current challenge. Evidently, increased understanding of molecular pathways and their connection to therapeutic outcomes will dramatically increase the complexity of treatment decision-making.

One of the prime questions clinicians face today is whether or not to augment treatment for patients with potentially resectable disease. In other words, can more patients be converted from unresectable to resectable by increasing combination therapy, including regimens that incorporate VEGF and EGFR inhibitors? Studies have shown that combining

these 2 classes of agents may significantly increase toxicity and also decrease efficacy.¹⁻³ Therefore, we need to better understand the mechanisms of action and interaction of these targeted agents. If their joint efficacy can be improved, it might be possible to offer more curative interventions, particularly for patients with limited liver disease. However, only by advancing our understanding of the types of patients who will benefit most from a particular treatment can we appropriately select patients with a higher chance of reaching curative resection status. It is crucial to find molecular markers to identify patients who may become resectable with tumor shrinkage following a given therapeutic intervention.

Increasingly, data suggest that the efficacy of targeted agents such as bevacizumab and cetuximab may depend on the specific combination employed. For example, the FOLFIRI and FOLFOX chemotherapy regimens are not interchangeable. Clinical trial findings suggest that bevacizumab plus FOLFOX leads to little or no increase in response rate compared with FOLFOX alone, whereas the pivotal trial combining bevacizumab plus IFL chemotherapy showed significant improvements in response rate, PFS, and overall survival compared with IFL alone.⁴⁻⁶

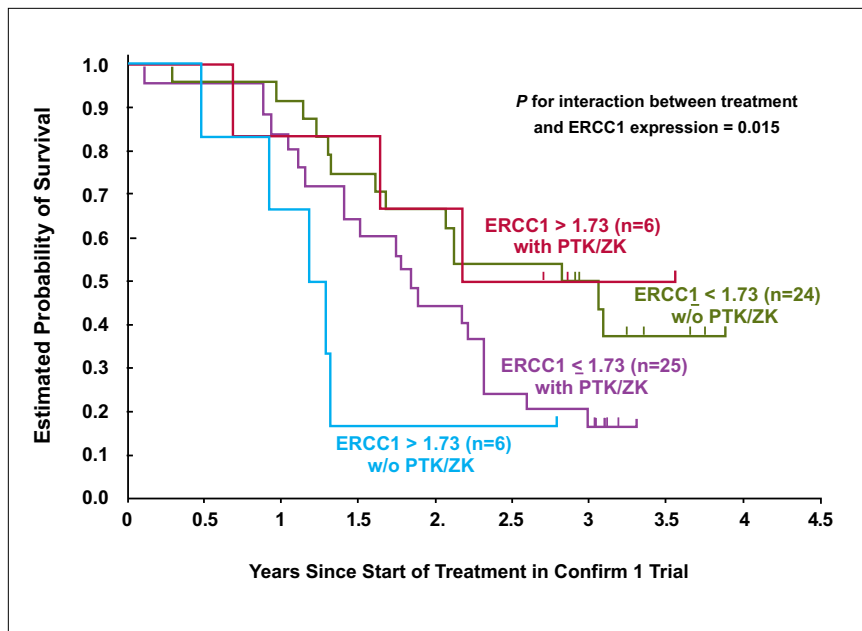


Figure 1. Confirm 1 Trial: ERCC1 gene expression levels are associated with outcome.

From Lenz et al. *J Clin Oncol.* 2008;26: Abstract 4131.

These findings need to be carefully considered when exploring treatment options for patients with metastatic colorectal cancer. In addition, we need to better understand the interactions of the VEGF and EGFR pathways with metabolic pathways associated with 5-FU, IFL, and DNA repair. For example, inhibition of EGFR can lead to decreased DNA repair.⁷

Mutant KRAS may increase not only VEGF but also DNA repair linking both the EGFR and VEGF pathways with ERCC-1, a marker for resistance to platinum-based therapy (unpublished data) (Figure 1).^{8,9} In the coming years, the selection of a targeted agent could be linked to a specific chemotherapeutic protocol.

Another direction for future research is increasing the predictive value of wild-type KRAS. Recent studies show an association between EGFR ligand expression and treatment outcomes among patients with wild-type KRAS treated with EGFR inhibitors (Figure 2).^{10,11} Results from these studies demonstrated that patients with high expression levels of epiregulin or amphiregulin had significantly higher response rates, longer PFS, and a 2-fold higher overall survival time compared with patients with low expression levels of these ligands. By contrast, the expression levels of epiregulin and amphiregulin did not affect outcomes among patients with mutant KRAS.

In addition, mutations in PI3K and loss of PTEN have been associated with resistance to EGFR inhibitors.^{12,13} Having a panel of markers—including KRAS, PI3K, PTEN, and EGFR ligands—available will make it more possible to predict the therapeutic value of EGFR inhibitors or other treatment options.

Currently in both Europe and the United States, clinical trials that explore the prospective testing of KRAS as a way to predict outcome with EGFR inhibitors are in the planning stages. As Dr. Chu mentioned, the NCI has initiated a task force to design clinical trials for patients with mutant KRAS. This task force is considering a 2-year period to conduct randomized phase II trials for which only patients with mutant

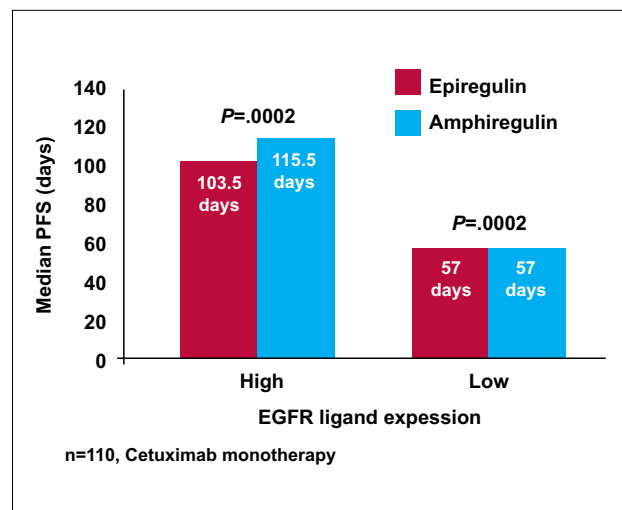


Figure 2. EGFR ligand expression: a predictor for increased PFS?

Adapted from Khambata-Ford S, et al. *J Clin Oncol.* 2007;25:3230-3237. EGFR=epidermal growth factor receptor; PFS=progression-free survival.

KRAS would be eligible. Agents that prove effective for this population in these studies would then move forward to a phase III trial. Due to the need for more treatment options for metastatic colorectal cancer patients with mutant KRAS, these studies will receive priority review.

With respect to VEGF, our understanding of which patient populations benefit most from these inhibitors is still very preliminary. There is no reliable biomarker yet identified for VEGF or VEGF receptor inhibitors. Only limited data are available regarding the efficacy of bevacizumab in combination with IFL for patients with mutant or wild-type KRAS. We need data from studies with larger patient samples and from those evaluating other chemotherapy regimens such as FOLFIRI and FOLFOX.

As Dr. Chu discussed, patients with mutant KRAS are the focus of novel drug development efforts. Drugs that inhibit pathways independent of KRAS will likely be developed for the treatment of metastatic colorectal cancer patients with mutant KRAS. Agents currently being evaluated for this population include Braf, insulin-like growth factor receptor (IGFR), and histone deacetylase inhibitors.

The future treatment of metastatic colorectal cancer is very bright and holds significant opportunities to select more effective and less toxic therapies.

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Slide Library

RAS Signal Transduction

✓ RAS is a G protein (GTPase) that cycles between active (RAS-GTP) and inactive (RAS-GDP) forms, thus acting as a binary switch for signal transduction from cell surface receptors (like EGFR).
 ✓ Activating mutations prevent GTP hydrolysis, causing RAS to be locked in the "on" position.

Reprinted with permission from Schubert S et al., *Nat Rev Cancer* 4:295-308, 2007.

EGFR and KRAS

EGFR = epidermal growth factor receptor.

Reprinted with permission from Khambata-Ford S, et al. *J Clin Oncol*, 2007.

KRAS Testing Methods

Methods	Description
Direct Sequencing	KRAS exon 2 was PCR amplified from the isolated DNA and the PCR products were directly sequenced
Allele-specific PCR	Utilizes allele-specific PCR amplification of 7 somatic mutations in codons 12 and 13 (ARMS); no tissue dissection performed
Direct Sequencing	Direct DNA sequencing of codons 12 and 13 with tumor tissue enrichment
Allele-specific hybridization	Allele-specific primer extensions for detecting mutations in codons 12 and 13 of the KRAS gene
Allele-specific hybridization	Allele-specific oligonucleotide hybridization for mutations in codons 12 and 13

PCR = polymerase chain reaction.

CRYSTAL Trial: Response Rate KRAS Wild Type vs Mutant

Response rate, %

■ Cetuximab + FOLFIRI
 ■ FOLFIRI

FOLFIRI = leucovorin, 5-fluorouracil, irinotecan.

CRYSTAL: Enhanced Efficacy of Cetuximab + FOLFIRI in Wild Type KRAS

	ITT		KRAS wild type		KRAS mutant	
	Cetuximab + FOLFIRI	FOLFIRI	Cetuximab + FOLFIRI	FOLFIRI	Cetuximab + FOLFIRI	FOLFIRI
n	599	599	172	176	105	87
ORR, %	47	39	59	43	36	40
P	.0038		.0025		.46	
PFS, median mo	8.9	8.0	9.9	8.7	7.6	8.1
HR	0.85		0.68		1.07	
P	.048		.017		.75	

FOLFIRI = leucovorin, 5-fluorouracil, irinotecan; HR = hazard ratio; ITT = intent-to-treat population; ORR = overall response rate; PFS = progression-free survival.

OPUS: Overall Response Rate KRAS Wild Type versus KRAS Mutant

Overall response rate, %

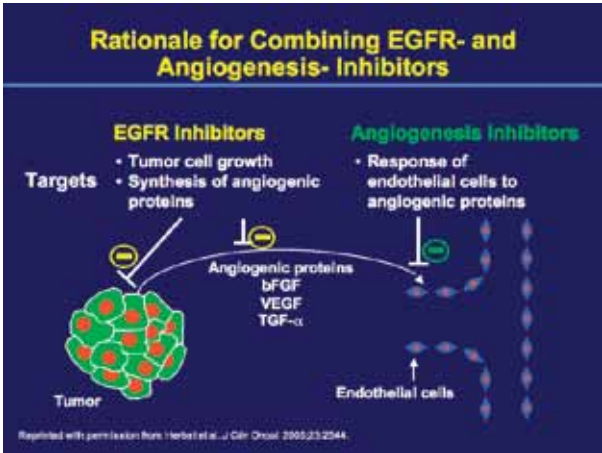
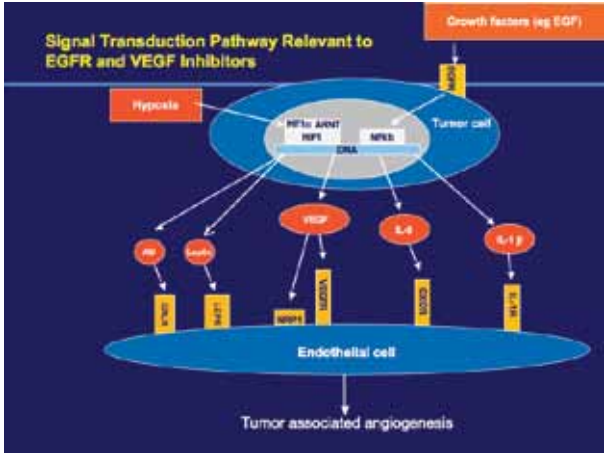
■ Cetuximab + FOLFOX
 ■ FOLFOX

FOLFOX = leucovorin, 5-fluorouracil, oxaliplatin.

KRAS Status: Predictive Value for Survival With Cetuximab Therapy

	n	ORR (all patients)	KRAS (wt)	ORR (wt)	Wild type (wt) vs mutant (mt) (KRAS evaluable population)	
					PFS, wk	OS, mo
Lillevre (2006)	30	37%	43%	6%	—	16 vs 7 (P=.016)
Di Fiore	59	20%	27%	6%	23.9 vs 13.0 (P<.015)	—
De Rooster*	113	25%	41%	6%	24 vs 12 (P=.074)	9.8 vs 8.3 (P=.020)
Lillevre (2006)	89	29%	27%	6%	31.4 vs 10.1 (P<.0001)	14.3 vs 10.1 (P=.020)

*In the combination therapy group (mt vs wt PFS=12 vs 34 weeks, P=0.01; OS=9.3 vs 10.3 months, P=0.03)
Lillevre A, et al. Cancer Res 2007;67:3992-3995; Di Fiore F, et al. Br J Cancer 2007;96:1186-1190; De Rooster T, et al. Ann Oncol 2007;18:3385-3390; Lillevre A, et al. J Clin Oncol 2006;24:374-379



PACCE study – FOLFIRI arms: PFS by KRAS status

	n	FOLFIRI + bev + pmab, PFS (med mo)	FOLFIRI + bev, PFS (med mo)
Iri-CT ITT set	230	10.1	11.7
KRAS efficacy set	200	10.0	12.3
Wild-type KRAS	115	10.0	14.5
Mutant KRAS	85	8.3	11.9

All wildtype KRAS patients did better, and those treated with FOLFIRI + BEV had PFS = 14.5 mos
Hecht JR et al. ASCO Q 2006
Bev = bevacizumab; FOLFIRI = leucovorin, 5-fluorouracil, irinotecan; PFS = progression-free survival; pmab = panitumumab.

- ### Anti-EGFR Antibodies: Take-Home Messages
- ◆ Cetuximab has been safely and effectively combined with Irinotecan and Oxaliplatin for first-, second-, and third-line treatment
 - ◆ Cetuximab is a reasonable treatment alternative to bevacizumab in the first-line and neoadjuvant setting (liver-limited disease)
 - ◆ Bevacizumab plus anti-EGFR antibody should not be used in combination with chemotherapy in first-line setting

- ### Conclusions: KRAS Status and Outcome
- Cetuximab added to chemotherapy in first-line metastatic colorectal cancer improves outcome of patients with wild-type KRAS
 - Irinotecan
 - Oxaliplatin
 - No benefit seen in patients with mutant KRAS
 - Enhanced clinical benefit of Cetuximab in wild-type KRAS now documented across all lines of metastatic colorectal cancer

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Notes

KRAS Mutation in Metastatic Colorectal Cancer and Its Impact On the Use of EGFR Inhibitors

CME Quiz: Circle the correct answer for each question below.

1. Approximately _____ of all colon tumors exhibit KRAS mutations.
 - a. 10–20%
 - b. 35–40%
 - c. 65%
 - d. 80–90%
2. The Ras/Raf/MAP kinase signaling pathway, which is constitutively activated by KRAS mutations, is directly associated with:
 - a. increased cell survival
 - b. promotion of cell growth
 - c. more rapid metastases
 - d. both a and b
3. In the CRYSTAL study, PFS among patients with wild-type KRAS treated with cetuximab plus FOLFIRI was:
 - a. 2.5 months
 - b. 6.5 months
 - c. 9.9 months
 - d. the same as PFS among wild-type KRAS patients treated with FOLFIRI alone
4. In the CRYSTAL study, PFS among patients with mutant KRAS who received cetuximab plus FOLFIRI was _____ the PFS among patients with mutant KRAS who received FOLFIRI alone.
 - a. nearly identical to
 - b. longer than
 - c. shorter than
 - d. Patients with mutant KRAS were not included in the CRYSTAL study
5. In a retrospective analysis of the OPUS study, the ORR among wild-type KRAS patients treated with cetuximab plus chemotherapy was:
 - a. 30%
 - b. 25%
 - c. 80%
 - d. 61%
6. Cetuximab is an appropriate choice for the first-line treatment of metastatic colorectal cancer patients with wild-type KRAS:
 - a. who are symptomatic from their tumor
 - b. who require significant tumor shrinkage to allow for potentially curative resection of liver metastases
 - c. for whom gain in survival time is the main goal of therapy
 - d. both a and b
7. In the PACCE study, the lack of benefit from the dual-antibody combination of panitumumab plus bevacizumab plus chemotherapy was seen among:
 - a. wild-type KRAS patients only
 - b. mutant KRAS patients only
 - c. all patients, regardless of KRAS status
 - d. None of the above.
8. In the CAIRO2 study, combining cetuximab with bevacizumab plus chemotherapy in the first-line setting:
 - a. did not provide additional benefits beyond bevacizumab plus chemotherapy alone
 - b. was associated with a statistically significantly longer OS compared with bevacizumab plus chemotherapy alone among wild-type KRAS patients
 - c. was associated with fewer adverse events among wild-type KRAS patients compared with cetuximab plus chemotherapy alone
 - d. was associated with a statistically significantly longer PFS than bevacizumab plus chemotherapy alone among mutant KRAS patients
9. ERCC-1 is a marker for:
 - a. resistance to EGFR inhibitors
 - b. resistance to platinum-based therapy
 - c. a high likelihood of response to VEGF inhibitors
 - d. a high likelihood of response to histone deacetylase inhibitors
10. Mutations in PI3K and loss of PTEN have been associated with:
 - a. resistance to EGFR inhibitors
 - b. resistance to platinum-based therapy
 - c. a high likelihood of response to mTOR inhibitors
 - d. rapidly progressing disease

Evaluation Form:

KRAS Mutation in Metastatic Colorectal Cancer and Its Impact on the Use of EGFR Inhibitors

To assist us in evaluating the effectiveness of this activity and to make recommendations for future educational offerings, please take a few minutes to complete this evaluation form. You must complete this evaluation form to receive acknowledgment for completing this activity.

Please answer the following questions by circling the appropriate rating:

1 = Strongly Disagree 2 = Disagree 3 = Neutral 4 = Agree 5 = Strongly Agree

Extent to Which Program Activities Met the Identified Objectives

After completing this activity, I am now better able to:

- | | | | | | |
|--|---|---|---|---|---|
| 1. Describe the importance of new study findings on the treatment of metastatic colorectal cancer (mCRC) as presented during the 2008 ASCO annual meeting. | 1 | 2 | 3 | 4 | 5 |
| 2. Explain the effect of KRAS mutation on the results of clinical trials evaluating new treatment options in mCRC. | 1 | 2 | 3 | 4 | 5 |
| 3. Identify which patients would respond best to newly available treatment options for mCRC, including EGFR inhibitors. | 1 | 2 | 3 | 4 | 5 |
| 4. Outline future research directions in the treatment of mCRC. | 1 | 2 | 3 | 4 | 5 |

Overall Effectiveness of the Activity

The content presented:

- | | | | | | |
|---|---|---|---|---|---|
| Was timely and will influence how I practice | 1 | 2 | 3 | 4 | 5 |
| Enhanced my current knowledge base | 1 | 2 | 3 | 4 | 5 |
| Addressed my most pressing questions | 1 | 2 | 3 | 4 | 5 |
| Provided new ideas or information I expect to use | 1 | 2 | 3 | 4 | 5 |
| Addressed competencies identified by my specialty | 1 | 2 | 3 | 4 | 5 |
| Avoided commercial bias or influence | 1 | 2 | 3 | 4 | 5 |

Impact of the Activity

Name one thing you intend to change in your practice as a result of completing this activity.

Please list any topics you would like to see addressed in future educational activities.

Additional comments about this activity.

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As part of our continuous quality improvement effort, we conduct postactivity follow-up surveys to assess the impact of our educational interventions on professional practice. Please indicate if you would be willing to participate in such a survey:

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Post-test Answer Key

1	2	3	4	5	6	7	8	9	10

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