

American Society of Clinical Oncology Provisional Clinical Opinion: Testing for *KRAS* Gene Mutations in Patients with Metastatic Colorectal Carcinoma to Predict Response to Anti-Epidermal Growth Factor Receptor Monoclonal Antibody Therapy

Carmen J. Allegra, J. Milburn Jessup, Mark R. Somerfield, Stanley R. Hamilton, Elizabeth H. Hammond, Daniel F. Hayes, Pamela K. McAllister, Roscoe F. Morton, and Richard L. Schilsky

Reprint requests:

American Society of Clinical Oncology

2318 Mill Road, Suite 800

Alexandria, VA 22314

e-mail: guidelines@asco.org

ABSTRACT

Purpose: An American Society of Clinical Oncology (ASCO) provisional clinical opinion (PCO) offers timely clinical direction to ASCO's membership following publication or presentation of potentially practice-changing data from major studies. This PCO addresses the utility of *KRAS* gene mutation testing in patients with metastatic colorectal carcinoma to predict response to anti-epidermal growth factor receptor (anti-EGFR) monoclonal antibody (MoAb) therapy with cetuximab or panitumumab (see Note).

Clinical Context: Recent results from phase II and III clinical trials demonstrate that patients with metastatic colorectal cancer benefit from therapy with MoAbs directed against the EGFR, when used either as monotherapy or combined with chemotherapy. Retrospective subset analyses of the data from these trials strongly suggest that patients who have *KRAS* mutations detected in codon 12 or 13 do not benefit from this therapy.

Recent Data: Five randomized controlled trials of cetuximab or panitumumab have evaluated outcomes for patients with metastatic colorectal carcinoma in relation to *KRAS* mutational status as no mutation detected (wild type) or abnormal (mutated). Another five single-arm studies have retrospectively evaluated tumor response according to *KRAS* status.

Provisional Clinical Opinion: Based on systematic reviews of the relevant literature, all patients with metastatic colorectal carcinoma who are candidates for anti-EGFR antibody therapy should have their tumor tested for *KRAS* mutations in a CLIA-accredited laboratory. If *KRAS* mutation in codon 12 or 13 is detected, then patients with metastatic colorectal carcinoma should not receive anti-EGFR antibody therapy as part of their treatment.

NOTE. ASCO's provisional clinical opinions (PCOs) reflect expert consensus based on clinical evidence and literature available at the time they are written, and are intended to assist physicians in clinical decision-making and identify questions and settings for further research. Due to the rapid flow of scientific information in oncology, new evidence may have emerged since the time a PCO was submitted for publication. PCOs are not continually updated and may not reflect the most recent evidence. PCOs cannot account for individual variation among patients, and cannot be considered inclusive of all proper methods of care or exclusive of other treatments. It is the responsibility of the treating physician or other health care provider, relying on independent experience and knowledge of the patient, to determine the best course of treatment for the patient. Accordingly, adherence to any PCO is voluntary, with the ultimate determination regarding its application to be made by the physician in light of each patient's individual circumstances. ASCO PCOs describe the use of procedures and therapies in clinical practice and cannot be assumed to apply to the use of these interventions in the context of clinical trials. ASCO assumes no responsibility for any injury or damage to persons or property arising out of or related to any use of ASCO's PCOs, or for any errors or omissions.

INTRODUCTION

The American Society of Clinical Oncology (ASCO) has established a rigorous, evidence-based approach—the provisional clinical opinion (PCO)—to offer a rapid response to emerging data in clinical oncology. The PCO is intended to offer timely clinical direction to ASCO’s oncologists following publication or presentation of potentially practice-changing data from major studies (Appendix).

This PCO addresses only the utility of testing for mutations in codons 12 or 13 of the *KRAS* gene in patients with metastatic colorectal carcinoma to predict response to anti-epidermal growth factor receptor (anti-EGFR) monoclonal antibody (MoAb) therapy; that is, cetuximab or panitumumab.

STATEMENT OF THE CLINICAL ISSUE

Results from phase II and III clinical trials of the anti-EGFR MoAbs cetuximab and panitumumab when used either as monotherapy or in combination with chemotherapy have shown that patients with metastatic colorectal carcinoma may benefit from these therapies, and both agents are approved by the US Food and Drug Administration (FDA) for treatment of metastatic colorectal cancer. Stratified analyses of data from these trials by *KRAS* mutational status—not detected (wild type) or abnormal (mutated)—indicated that patients with *KRAS* mutation in codon 12 or 13 did not derive benefit from treatment with cetuximab or panitumumab.

ASCO’S PROVISIONAL CLINICAL OPINION

Based on a systematic review of the relevant literature, all patients with metastatic colorectal carcinoma who are candidates for anti-EGFR monoclonal antibody therapy should have their tumor tested for *KRAS* mutations in a CLIA-accredited laboratory. If *KRAS* mutation in codon 12 or 13 is detected, then patients with metastatic colorectal carcinoma should not receive anti-EGFR monoclonal antibody therapy as part of their treatment.

LITERATURE REVIEW AND ANALYSIS

The review of the evidence on which this PCO is based consists primarily of the rigorous systematic review of the literature conducted by the Blue Cross and Blue Shield Association (BCBSA) Technology Evaluation Center (TEC).¹⁻¹⁰ Details of the BCBSA TEC assessment can be found in the full TEC report, which is available at www.bcbs.com/blueresources/tec/press/kras-mutations-epidermal.html. In summary, the TEC searched MEDLINE through October 2008 to identify all relevant articles on anti-EGFR MoAb therapy and *KRAS* mutation analysis. The TEC supplemented its review by searching for relevant abstracts from the ASCO 2008 Annual Meeting via the online database (www.asco.org/vm).

Studies were included in the TEC assessment if they were peer-reviewed, full-length, English-language articles and investigated response to anti-EGFR MoAbs among patients with metastatic colorectal cancer with respect to *KRAS* mutational status. The TEC also included phase II and III randomized clinical trials from the 2008 ASCO Annual Meeting if the full presentation slides were available online.

The TEC review identified post hoc analyses on subsets from five randomized, controlled trials (RCTs) of cetuximab or panitumumab that evaluated outcomes for patients with metastatic colorectal cancer in relation to *KRAS* mutational status (Table 1); and five single-arm studies that retrospectively evaluated treatment response according to *KRAS* status (Table 2). Two broad findings emerged from the TEC assessment of these studies: (1) a consistent correlation between presence of a *KRAS* mutation in codon 12 or 13 and lack of response to anti-EGFR MoAb therapy in patients with metastatic colorectal cancer, and (2) evidence of improved tumor response, progression-free, and/or overall survival in response to anti-EGFR MoAb therapy only in those patients with no mutation in codon 12 or 13 (wild type) versus abnormal (mutated) *KRAS* tumors in analyses from four of five RCTs.

Oncologists should understand that both the PCO and the TEC review are based on assays that detect mutations in codons 12 and 13 of *KRAS* only. Mutations also occur, although uncommonly, at codons 61 and 146, and these also activate *KRAS*. In addition, the PCO and the TEC review do not evaluate the differences in sensitivity and specificity among the various assays that are available for *KRAS* mutation testing. (See excerpt from the College of American Pathologists Perspectives on Emerging Technology [POET] Report on *KRAS* mutation testing, below.) The oncologist is encouraged to discuss these issues with the Director of his/her clinical laboratory. Finally, this PCO is limited to the current state of knowledge about the treatment of metastatic colorectal carcinoma and does not address the use of anti-EGFR MoAbs for adjuvant therapy in colorectal carcinoma, the use of small molecule tyrosine kinase inhibitors in metastatic colorectal carcinoma, or assays for other alterations that have been reported to affect response to anti-EGFR MoAbs (e.g., mutation in *BRAF*,^{2,11,12} *PI3K*,^{13,14} or *PTEN*¹⁴ genes and loss of expression of *PTEN*¹⁵ that may indicate resistance; amplification of EGFR,¹⁶ lack of amplification of *PTEN*,¹⁷ and expression of epiregulin or amphiregulin⁷ that may indicate response). These subjects are either the focus of current research, or there are insufficient data to justify an opinion at present.¹⁸

Table 1. Randomized Clinical Trial Evidence on Relationship of *KRAS* Mutation Status to Efficacy of anti-EGFR Monoclonal Antibodies in Patients With Metastatic Colorectal Cancer

Study and Population	Treatments by Arm	Variable	<i>KRAS</i> WT		<i>KRAS</i> Mutated	
			Antibody Arm	Control Arm	Antibody Arm	Control Arm
van Cutsem et al, 2008 ¹⁰ ; CRYSTAL trial of first line therapy	FOLFIRI ± cetuximab	No. of patients	172	176	105	87
		Response rate, %	59.3	43.2	36.2	40.2
		95% CI <i>P</i>	51.6 to 66.7	35.8 to 50.9	27.0 to 46.2	29.9 to 51.3
		Median PFS, months HR	9.9	8.7	7.6	8.1
		<i>P</i>	.0025		.46	
Bokemeyer et al, 2008 ³ ; OPUS trial of first line therapy	FOLFOX ± cetuximab	No. of patients	61	73	52	47
		Response rate, %	60.7	37.0	32.7	48.9
		95% CI <i>P</i> OR	47.3 to 72.9	26.0 to 49.1	20.3 to 47.1	34.1 to 63.9
		95% CI	1.24 to 5.23		0.22 to 1.15	
		Median PFS, months HR <i>P</i>	7.7	7.2	5.5	8.6
Punt et al, 2008 ⁹ ; CAIRO2 trial of first line therapy	(Capecitabine + oxaliplatin + bevacizumab) ± cetuximab	No. of patients	153	152	93	103
		Median PFS, months <i>P</i>	10.5	10.7	8.6	12.5
		Median OS, months <i>P</i>	22.2	23.0	19.1	24.9
Amado et al, 2008 ¹ ; chemotherapy-refractory disease	Panitumumab v best supportive care	No. of patients	124	119	84	100
		Response rate, %	17	0	0	0
		Median PFS, weeks HR	12.3	7.3	7.4	7.3
		95% CI	0.45 0.34 to 0.59		0.99 0.73 to 1.36	
Karapetis et al, 2008 ⁶ ; second- or subsequent-line therapy	Cetuximab v best supportive care	No. of patients	117	113	81	83
		Response rate, %	12.8	0	1.2	0
		Median PFS, months HR	3.7	1.9	1.8	1.8
		95% CI <i>P</i>	0.40 0.30 to 0.54 < .001		0.99 0.73 to 1.35 .96	
		Median OS, months <i>P</i>	9.5	4.8	4.5	4.6
			.01 (for interaction, <i>KRAS</i> mutation status × treatment arm)			

		OS at 1 year, %	28.3	20.1	13.2	19.6
		HR (death)	0.55		0.98	
		95% CI	0.41 to 0.74		0.70 to 1.37	
		<i>P</i>	< .001		.89	

Abbreviations: EGFR, epidermal growth factor receptor; WT, wild type; HR, hazard ratio; OR, odds ratio; PFS, progression-free survival; FOLFIRI, folinic acid, fluorouracil, and irinotecan; FOLFOX, folinic acid, fluorouracil, and oxaliplatin; CRYSTAL, Cetuximab Combined With Irinotecan in First-Line Therapy for Metastatic Colorectal Cancer; OPUS, Oxaliplatin and Cetuximab in First-Line Treatment of mCRC; CAIRO2, Capecitabine, Irinotecan, and Oxaliplatin in Advanced Colorectal Cancer (2).

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Table 2. Single-Arm Studies of Treatment of Metastatic CRC With Anti-EGFR Monoclonal Antibodies and *KRAS* Mutational Status

Study and Population	Treatments by Arm	Variable	<i>KRAS</i> WT	<i>KRAS</i> Mutated
Lievre et al. 2008 ⁸ ; second-line therapy	Cetuximab	No. of patients	65	24
		Response rate	40	0
		<i>P</i>	.001	
		PFS, weeks	31.4	10.1
		95% CI	19.4 to 36	8 to 16
		<i>P</i>	.0001	
		OS, months	14.3	10.1
		95% CI	9.4 to 20	5.1 to 13
		<i>P</i>	.026	
De Roock et al, 2008 ⁴	Cetuximab (C) alone v with irinotecan (I)	No. of patients	57	46
		Response rate	41	0
		<i>P</i> (C + I)	.000001	
		<i>P</i> (C alone)	.126	
		PFS C + I, weeks	34	12
		95% CI	28.5 to 40.0	5.4 to 18.7
		<i>P</i>	.016	
		PFS C, weeks	12	12
95% CI	4.2 to 20.0	7.0 to 17.0		
<i>P</i>	.351			
OS C + I, weeks	44.7	27.3		
95% CI	28.4 to 61.0	9.5 to 45.0		
<i>P</i>	.003			
OS, weeks	27	25.3		
95% CI	8.9 to 45.1	0.0 to 70.0		
<i>P</i>	.330			
Khambata-Ford et al. 2007 ⁷	Cetuximab; second- or third-line treatment	No. of patients	50	30
		Response rate, %	10	0
Di Fiore et al, 2007 ⁵	Cetuximab plus chemotherapy	No. of patients	43	16
		Response rate, %	28	0

Benvenuti et al, 2007 ²	Panitumumab or cetuximab or cetuximab plus chemotherapy	No. of patients	32	16
		Response rate, %	31	6

Abbreviations: CRC, colorectal cancer; WT, wild type; PFS, progression-free survival; OS, overall survival.

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SUMMARY OF COLLEGE OF AMERICAN PATHOLOGISTS PERSPECTIVES ON EMERGING TECHNOLOGY (POET) REPORT ON *KRAS* MUTATION TESTING

Under a reciprocal arrangement with the College of American Pathologists (CAP), ASCO is reprinting key elements of a CAP Perspectives on Emerging Technology Report (POET) on *KRAS* mutation testing for colorectal cancer as a service to the ASCO membership. The CAP POET was developed by an ad hoc panel and offers state-of-the-art information on *KRAS* testing for the CAP membership. The full CAP document can be found at www.cap.org/POET.

CAP *KRAS* Specimen and Test Information

Acceptable Sample Types

(The samples should be specifically chosen by a pathologist to include predominantly tumor cells without significant necrosis or inflammation.)

- Freshly extracted from patient, provided fresh or in RNA preservation solution, such as *RNAlater*
- Freshly extracted from patient and rapidly frozen and stored frozen
- Neutral buffered formalin fixed and paraffin embedded, area of interest selected specifically by the pathologist

Acceptable Assay Types

In all cases, DNA is first extracted by laboratory-specific and standardized protocols that incorporate standards to assure adequate and specific extraction.

- *Real-Time Polymerase Chain Reaction.* In real-time polymerase chain reaction (PCR), fluorescent probes specific for the most common mutations in codons 12 and 13 are utilized. When a mutation is present, the probe binds and fluorescence is detected.
- *Direct Sequencing Analysis.* *KRAS* mutations can also be identified using a direct sequencing method of exon 1 in the *KRAS* gene. This technique identifies all possible mutations in the exon.
- At this time, there are no FDA-approved tests for *KRAS* testing, but *KRAS* testing can be performed using laboratory-developed tests. Outside the United States, a United Kingdom-based company, DxS, offers a kit (TheraScreen) for its *KRAS* mutations assay. DxS and other vendors are expected to seek FDA approval for their assays.
- Choice of assay defined by which assay the laboratory has validated and routinely uses. Oncologist should consult with laboratory about specific test name to order.

Assay Reporting

***KRAS* Normal:**

No mutation identified. Report will specify assay type and controls used.

***KRAS* Abnormal:**

Treatment with anti-EGFR monoclonal antibody therapy is *not* recommended based on ASCO Provisional Clinical Opinion. Mutation found. Report will specify what mutation was found, what assay was done, and what controls were used.

APPENDIX

OVERVIEW OF THE PROVISIONAL CLINICAL OPINION DEVELOPMENT PROCESS

PCO Topic Selection

The ASCO Health Services Committee (HSC) leadership is responsible for accepting, reviewing, and approving proposed PCO topics on behalf of the ASCO Board of Directors. The selection of this PCO topic was guided by the Topic Selection Algorithm that is used by the HSC to guide selection of topics for ASCO's clinical practice guidelines (www.asco.org/guidelines/manual).

PCO Evidentiary Basis

Provisional clinical opinions are informed by expeditious methodological assessments of the data in question. To this end, ASCO has established a relationship with the National Cancer Institute's Physician Data Query (PDQ) Editorial Boards. The PDQ's Editorial Boards are comprised of content experts in oncology and related specialties. Upon request from ASCO, the relevant PDQ Editorial Board will provide a written assessment of the new data.

For the present PCO, however, ASCO learned that the Blue Cross and Blue Shield Association (BCBSA) Technology Evaluation Center (TEC) was conducting a technology assessment, including a comprehensive systematic review of the available evidence, on the topic of *KRAS* mutations and anti-EGFR monoclonal antibody in metastatic colorectal cancer. BCBSA TEC made the technology assessment available to ASCO for use in developing this PCO.

Ad Hoc PCO Panel

The BCBSA TEC Assessment was forwarded to an ad hoc panel that was selected and charged by the HSC to draft the PCO. The ad hoc panel includes six content experts and a patient representative. The membership of the ad hoc panel was chosen in accordance with ASCO's Conflicts of Interest Management Procedures for Clinical Practice Guidelines (COI Procedures). The COI Procedures call for the majority of ad hoc panel members to have no relationships with companies potentially affected by the PCO, and generally require ad hoc panel co-chairs to be free from relationships with affected companies.

PCO Review and Approval

The PCO was approved by a unanimous vote of (1) the ad hoc panel members; (2) the HSC leadership (Past-Chair, Chair, Chair-Elect, and Board Liaison) and selected content experts drawn from the HSC membership; and (3) a subset of the ASCO Board (Past-President, President, President-Elect) and selected content experts drawn from the Board membership and appointed at the discretion of the President.

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