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ORIGINAL RESEARCH

Uptake of *KRAS* mutation testing in patients with metastatic colorectal cancer in Europe, Latin America and Asia

Fortunato Ciardiello · Sabine Tejpar · Nicola Normanno · Domenica Mercadante · Tracey Teague · Bruno Wohlschlegel · Eric Van Cutsem

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Abstract The mutation status of the *KRAS* gene in the tumors of patients with metastatic colorectal cancer (mCRC) is a predictive biomarker for the efficacy of epidermal growth factor receptor monoclonal antibody therapy. The establishment of *KRAS* mutation testing in this setting represents a significant change to standard diagnostic procedures and a major advance in the personalization of cancer care. Against a changing regulatory background, three cross-sectional surveys of physicians in 14 countries in Europe, Latin America and Asia were conducted in 2008, 2009, and 2010 to investigate the uptake and outcome of *KRAS* testing for patients with mCRC. Physicians in each year answered questions on four patients (last patient seen and last seen in first-, second- and third-line settings). Fieldwork was carried out February–May 2008, January–April 2009, and January–April 2010. Data from 3,819, 3,740 and 3,820 anonymized, uncoded patient records were collated. The frequency of *KRAS* testing in patients with mCRC increased from 3% in 2008 to 47% in 2009 and 69% in 2010. The 2010 survey revealed that test results were available within 15 days for 82%, 51% and 98% of the 1679, 679, and 261 tested patients in the European, Latin American and Asian regions, respectively. Cetuximab was the most commonly administered targeted agent in tested patients with *KRAS* wild-type mCRC (798/1607 patients; 50%) and bevacizumab was the most commonly administered targeted agent in tested patients with *KRAS* mutant tumors (396/893; 44% overall). In conclusion, *KRAS* testing is now widely established as a routine diagnostic procedure for patients with mCRC and is used increasingly to guide treatment selection.

Keywords KRAS · Predictive · EGFR · Cetuximab · Metastatic colorectal cancer · mCRC

F. Ciardiello (✉)
Division of Medical Oncology, Department of Experimental and Clinical Medicine and Surgery "F. Magrassi and A. Lanzara", Second University of Naples,
Via S. Pansini 5,
80131 Naples, Italy
e-mail: fortunato.ciardiello@unina2.it

S. Tejpar · E. Van Cutsem
Digestive Oncology Unit, University Hospital Gasthuisberg, Leuven, Belgium

N. Normanno
Cell Biology and Biotherapy Unit, INT-Fondazione Pascale, Naples, Italy

D. Mercadante
IMS Health,
Milan, Italy

T. Teague · B. Wohlschlegel
Merck KGaA,
Darmstadt, Germany

Introduction

The identification of molecular characteristics of tumors that are predictors of clinical outcome in response to treatment will increasingly allow for the tailoring of anticancer therapy on an individual patient basis. Such predictive biomarkers may conceivably take the form of mutational, copy number, epigenetic or expression changes of specific genes or may be more complex marker systems, perhaps incorporating transcript or proteomic expression profiles [1–3].

The potential of such approaches has been established in relation to the treatment of metastatic colorectal cancer (mCRC) by studies demonstrating that the clinical efficacy

of epidermal growth factor receptor (EGFR)-targeting monoclonal antibodies is dependent on whether tumors carry mutations in codon 12 or 13 of the *KRAS* gene [4, 5], which encodes a downstream effector of EGFR signaling. Initial observations in single-arm studies [6–13] suggested that the activity of cetuximab and panitumumab was limited to patients whose tumors were wild type for *KRAS*. This hypothesis was subsequently confirmed in retrospective and prospective analyses of tumor tissues collected during the course of randomized phase III studies [14–18]. These analyses have resulted in changes to the regulatory approval of cetuximab and panitumumab with the net effect being that these agents are now not recommended by the European Medicines Agency (EMA) or the Food and Drug

Table 1 Specialty of physicians interviewed in the 2009 and 2010 surveys according to region and country

Year, region, country	All physicians	Physician specialties, N (%)							
		Oncologist	Gastroenterologist	Internist	Radiotherapist	Oncology physician	Oncology surgeon	Oncologist/ hematologist	Surgeon
2009 survey									
Europe	528	458 (87)	53 (10)	17 (3)					
France	100	55 (55)	45 (45)						
Germany	100	100 (100)							
Italy	100	100 (100)							
Spain	100	100 (100)							
Austria	33	25 (76)		8 (24)					
Belgium	35	26 (74)	8 (23)	1 (3)					
Portugal	40	32 (80)		8 (20)					
Switzerland	20	20 (100)							
Latin America	275	275 (100)							
Argentina	50	50 (100)							
Brazil	125	125 (100)							
Mexico	50	50 (100)							
Venezuela	50	50 (100)							
Asia	150					72 (48)	28 (19)	25 (17)	25 (17)
China	100					72 (72)	28 (28)		
Taiwan	50							25 (50)	25 (50)
2010 survey									
Europe	538	477 (89)	52 (10)	8 (1)	1 (0.2)				
France	100	69 (69)	31 (31)						
Germany	100	98 (98)	2 (2)						
Italy	101	101 (100)							
Spain	100	100 (100)							
Austria	34	28 (82)	6 (18)						
Belgium	40	25 (63)	13 (33)	1 (3)	1 (3)				
Portugal	40	33 (83)		7 (18)					
Switzerland	23	23 (100)							
Latin America	276	275 (100)		1 (0.4)					
Argentina	50	49 (98)		1 (2)					
Brazil	125	125 (100)							
Mexico	51	51 (100)							
Venezuela	50	50 (100)							
Asia	150					59 (39)	41 (27)	25 (17)	25 (17)
China	100					59 (59)	41 (41)		
Taiwan	50							25 (50)	25 (50)

Administration for the treatment of mCRCs that carry mutations of the *KRAS* gene [19–22].

Mutations of the *KRAS* gene occur at an early stage of colorectal cancer development [23–26]. As early mutations, they are therefore likely to be found both in the primary tumor and also in the patient's metastatic lesions. Indeed, a series of studies comparing the mutation status of paired mCRC samples from the primary tumor and metastatic sites have found a high degree of concordance in relation to the absence or presence and type of mutation [27–29]. These factors, coupled with the restricted locations within the gene that activating mutations tend to be found [30] make *KRAS* testing of mCRCs in the clinical setting a relatively straightforward proposition [31, 32].

In order to investigate how effectively awareness of *KRAS* testing has penetrated routine clinical practice and to measure how many patients with mCRC now receive such tests, surveys of physicians practicing in this area in three different geographical regions were carried out between 2008 and 2010. Also examined on an individual patient basis for 2009 and 2010 were how quickly the test results were available, what those results were, and according to *KRAS* mutation status, which targeted agents the patients subsequently received. In the 2010 survey, the time at which patients were tested in the treatment continuum was also recorded.

Methods

Demographics

Cohorts of physicians with a minimum of 3 and a maximum of 35 years of specialist experience who were involved in the treatment of patients with mCRC at a range of different types of clinical centers in 14 countries were invited to take part in surveys that were designed to assess the physician's use of tumor *KRAS*-mutation testing, their current practice regarding such tests, and outcomes in relation to testing procedures. The study sponsor was identified to the participating physicians as "a major pharmaceutical company conducting the survey to help them learn more about this treatment area." For the purpose of analysis, summary data from individual country sets were grouped either together (*all countries*), or into three regional datasets—*Europe*: Austria, Belgium, France, Germany, Italy, Portugal, Spain, Switzerland; *Latin America*: Argentina, Brazil, Mexico, Venezuela; and *Asia*: China, Taiwan.

Survey procedures

This was a quantitative study completed in face-to-face interviews lasting approximately 50 min using structured questionnaires. Physicians were asked a series of questions, and the interviewer recorded their answers. Fieldwork was carried out initially February–May 2008 and repeated with different representative cohorts of physicians January–April 2009 and January–April 2010.

For each year of the survey, data relating to four anonymized, uncoded patient records were collected from each participating physician. These records were to be from the last patient the physician had seen with mCRC, and other than this patient, the last patient seen with mCRC who had started or was about to start first-line therapy, the last patient seen with mCRC who had started or was about to start second-line therapy, and the last patient seen with

Table 2 Anonymized, uncoded patient records considered by participating physicians according to region and line of therapy

Region, line of therapy	Patient records, N		
	2008	2009	2010
Europe	2146	2101	2145
First-line	937	955	956
Second-line	622	603	623
Third-line	587	543	566
Latin America	1086	1040	1083
First-line	498	488	455
Second-line	319	325	346
Third-line	269	227	282
Asia	587	599	592
First-line	265	281	267
Second-line	183	186	180
Third-line	139	132	145
All countries	3819	3740	3820
First-line	1700	1724	1678
Second-line	1124	1114	1149
Third-line	995	902	993

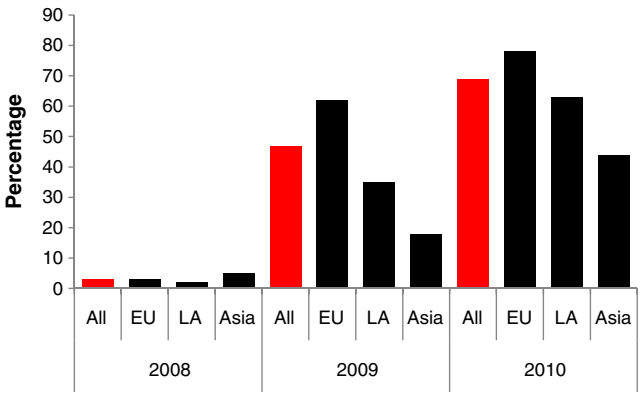


Fig. 1 Percentage of all patients and those in each regional group whose tumors were reported as tested for *KRAS* mutation status in the 2008, 2009 and 2010 surveys

mCRC who had started or was about to start third-line therapy. Data collected for each patient, in each survey year, included whether a *KRAS* mutation test was carried out on tumor tissue from the patient and what the result of that test was. For the 2009 and 2010 surveys, the time taken to obtain the test result was also recorded as well as information regarding the timing of the test in relation to line of therapy. For all patients, whether they received treatment including cetuximab, bevacizumab or panitumumab according to line of therapy was noted.

In addition to these patient-specific data, particular questions in the 2010 survey evaluated the physician's perceptions in relation to this area. In particular, physicians were asked whether they would routinely conduct a test for tumor *KRAS* status at the time of diagnosis of mCRC.

Table 3 Numbers of patients whose tumors were tested for *KRAS* mutation status and test outcomes in the 2009 and 2010 surveys

Year, region, line of therapy	Patients, N (%)[a]			*KRAS* test results, N (%)		
	All	Not tested	Tested	Tests with results[b]	*KRAS* wild-type[c]	*KRAS* mutant[c]
2009 survey[d]						
Europe	2101	793 (38)	1302 (62)	1264 (97)	783 (62)	481 (38)
First-line	955	441 (46)	512 (54)	487 (95)	283 (58)	204 (42)
Second-line	603	207 (34)	393 (65)	386 (98)	226 (59)	160 (41)
Third-line	543	145 (27)	397 (73)	391 (98)	274 (70)	117 (30)
Latin America	1040	676 (65)	364 (35)	329 (90)	200 (61)	129 (39)
First-line	488	334 (68)	154 (32)	127 (82)	78 (61)	49 (39)
Second-line	325	201 (62)	124 (38)	119 (96)	73 (61)	46 (39)
Third-line	227	141 (62)	86 (38)	83 (97)	49 (59)	34 (41)
Asia	599	488 (81)	109 (18)	108 (99)	82 (76)	26 (24)
First-line	281	233 (83)	48 (17)	47 (98)	32 (68)	15 (32)
Second-line	186	153 (82)	32 (17)	32 (100)	26 (81)	6 (19)
Third-line	132	102 (77)	29 (22)	29 (100)	24 (83)	5 (17)
All countries	3740	1957 (52)	1775 (47)	1701 (96)	1065 (63)	636 (37)
First-line	1724	1008 (58)	714 (41)	661 (93)	393 (59)	268 (41)
Second-line	1114	561 (50)	549 (49)	537 (98)	325 (61)	212 (39)
Third-line	902	388 (43)	512 (57)	503 (98)	347 (69)	156 (31)
2010 survey						
Europe	2145	466 (22)	1679 (78)	1609 (96)	1027 (64)	582 (36)
First-line	956	256 (27)	700 (73)	649 (93)	385 (59)	264 (41)
Second-line	623	118 (19)	505 (81)	489 (97)	312 (64)	177 (36)
Third-line	566	92 (16)	474 (84)	471 (99)	330 (70)	141 (30)
Latin America	1083	404 (37)	679 (63)	632 (93)	377 (60)	255 (40)
First-line	455	185 (41)	270 (59)	242 (90)	137 (57)	105 (43)
Second-line	346	126 (36)	220 (64)	209 (95)	130 (62)	79 (38)
Third-line	282	93 (33)	189 (67)	181 (96)	110 (61)	71 (39)
Asia	592	331 (56)	261 (44)	259 (99)	203 (78)	56 (22)
First-line	267	162 (61)	105 (39)	103 (98)	76 (74)	27 (26)
Second-line	180	105 (58)	75 (42)	75 (100)	57 (76)	18 (24)
Third-line	145	64 (44)	81 (56)	81 (100)	70 (86)	11 (14)
All countries	3820	1201 (31)	2619 (69)	2500 (95)	1607 (64)	893 (36)
First-line	1678	603 (36)	1075 (64)	994 (92)	598 (60)	396 (40)
Second-line	1149	349 (30)	800 (70)	773 (97)	499 (65)	274 (35)
Third-line	993	249 (25)	744 (75)	733 (99)	510 (70)	223 (30)

[a] Percentages relate to all patients for each region and all patients for each line of therapy

[b] Percentages relate to number of patients tested. Missing test results were either not yet available or else the test was judged to be invalid

[c] Percentages relate to number of tests with results

[d] Information was not available for 6 patients in Europe and 2 in Asia

Statistical methods

Physicians at consultant or senior registrar level (or equivalent) were selected for interview randomly from a range of institutions chosen as representative of the treatment landscape of the different geographical regions. All statistical tests were exploratory. The incidences of *KRAS* tumor mutations in regional groups and treatment settings and the year-on-year frequency of testing were compared using 2×2 contingency tables and Fisher's exact

Table 4 Numbers of patients whose tumors were tested for *KRAS* mutation status and test outcomes in the 2009 and 2010 surveys according to region and country

Year, region, country	Patients, N (%)[a]			*KRAS* test results, N (%)		
	All	Not tested	Tested	Tests with results[b]	*KRAS* wild-type[c]	*KRAS* mutant[c]
2009 survey[d]						
Europe	2101	793 (38)	1302 (62)	1264 (97)	783 (62)	481 (38)
France	400	105 (26)	295 (74)	282 (96)	192 (68)	90 (32)
Germany	400	131 (33)	269 (67)	264 (98)	168 (64)	96 (36)
Italy	396	229 (58)	167 (42)	164 (98)	102 (62)	62 (38)
Spain	400	104 (26)	296 (74)	293 (99)	145 (49)	148 (51)
Austria	127	46 (36)	81 (64)	78 (96)	55 (71)	23 (29)
Belgium	140	54 (39)	82 (59)	80 (98)	51 (64)	29 (36)
Portugal	160	92 (58)	68 (43)	60 (88)	36 (60)	24 (40)
Switzerland	78	32 (41)	44 (56)	43 (98)	34 (79)	9 (21)
Latin America	1040	676 (65)	364 (35)	329 (90)	200 (61)	129 (39)
Argentina	200	94 (47)	106 (53)	93 (88)	58 (62)	35 (38)
Brazil	475	316 (67)	159 (33)	155 (97)	86 (55)	69 (45)
Mexico	177	136 (77)	41 (23)	37 (90)	22 (59)	15 (41)
Venezuela	188	130 (69)	58 (31)	44 (76)	34 (77)	10 (23)
Asia	599	488 (81)	109 (18)	108 (99)	82 (76)	26 (24)
China	399	323 (81)	74 (19)	74 (100)	50 (68)	24 (32)
Taiwan	200	165 (83)	35 (18)	34 (97)	32 (94)	2 (6)
2010 survey						
Europe	2145	466 (22)	1679 (78)	1609 (96)	1027 (64)	582 (36)
France	400	48 (12)	352 (88)	335 (95)	229 (68)	106 (32)
Germany	400	117 (29)	283 (71)	278 (98)	202 (73)	76 (27)
Italy	404	107 (26)	297 (74)	286 (96)	176 (62)	110 (38)
Spain	400	80 (20)	320 (80)	314 (98)	159 (51)	155 (49)
Austria	130	12 (9)	118 (91)	114 (97)	73 (64)	41 (36)
Belgium	160	27 (17)	133 (83)	122 (92)	82 (67)	40 (33)
Portugal	160	49 (31)	111 (69)	96 (86)	63 (66)	33 (34)
Switzerland	91	26 (29)	65 (71)	64 (98)	43 (67)	21 (33)
Latin America	1083	404 (37)	679 (63)	632 (93)	377 (60)	255 (40)
Argentina	200	63 (32)	137 (69)	130 (95)	95 (73)	35 (27)
Brazil	480	200 (42)	280 (58)	263 (94)	149 (57)	114 (43)
Mexico	204	72 (35)	132 (65)	128 (97)	48 (38)	80 (63)
Venezuela	199	69 (35)	130 (65)	111 (85)	85 (77)	26 (23)
Asia	592	331 (56)	261 (44)	259 (99)	203 (78)	56 (22)
China	392	271 (69)	121 (31)	119 (98)	87 (73)	32 (27)
Taiwan	200	60 (30)	140 (70)	140 (100)	116 (83)	24 (17)

[a] Percentages relate to all patients for each region/country

[b] Percentages relate to number of patients tested. Missing test results were either not yet available or else the test was judged to be invalid

[c] Percentages relate to number of tests with results

[d] Information was not available for 6 patients in Europe and 2 in Asia

tests (GraphPad Software, La Jolla, California). All reported *p*-values are two-sided and given the exploratory nature of the analyses, have not been adjusted for the multiplicity of testing.

Results

Physician and patient demographics

The survey data were pooled for all countries and according to three geographical regions, Europe, Latin America, and Asia. As summarized in Table 1 according to region and country, the majority of the physicians surveyed in 2009 and 2010 were classified as oncologists, but also included were those identified as oncology physicians, gastroenterologists, oncology surgeons, oncologist/hematologists, surgeons, internists and radiotherapists. The physician's host institutions included public and private hospitals and specialist oncology centers. These institutions were located across a wide geographical distribution in each included country.

In 2008, 2009 and 2010, after interviews had been conducted with the participating physicians and questionnaires had been evaluated in quality control processes, the data from 3,819, 3,740 and 3,820 anonymized, uncoded patient records were collated. With reference to the patient's line of therapy, these records are summarized for all countries and according to region in Table 2. In each year, for each region, and reflecting the survey patient selection design and the greater number of patients in clinical practice receiving earlier lines of therapy, there were more records included from patients who were receiving first-line compared with second-line compared with third-line treatment.

Frequency of *KRAS* testing

In 2008, tumor *KRAS* mutation tests were performed for only 113 of 3,819 included patients (3%). This frequency

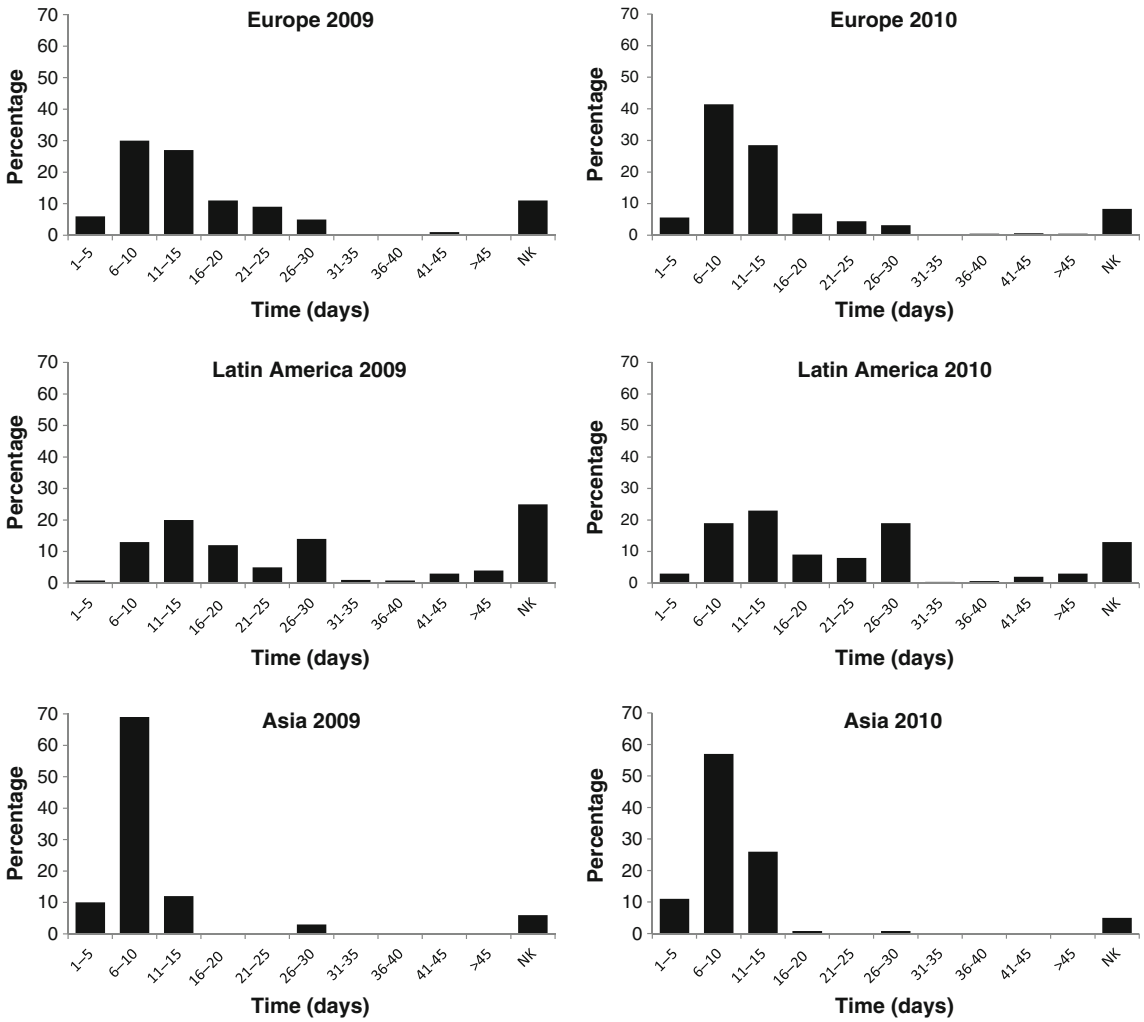


Fig. 2 Length of time to obtain *KRAS* test results in 2009 and 2010 according to region. *NK* not known

Table 5 Length of time to obtain *KRAS* mutation test results in 2009 and 2010 according to region and country

Year, region, country	Tests, N	Number of days to obtain test result, N (%)										
		1–5	6–10	11–15	16–20	21–25	26–30	31–35	36–40	41–45	>45	NK
2009 survey												
Europe	1302	77 (6)	387 (30)	347 (27)	143 (11)	121 (9)	66 (5)	2 (0.2)	3 (0.2)	17 (1)	1 (0.1)	138 (11)
France	295	5 (2)	47 (16)	79 (27)	18 (6)	74 (25)	38 (13)	2 (0.7)	1 (0.3)	16 (5)	1 (0.3)	14 (5)
Germany	269	28 (10)	83 (31)	62 (23)	21 (8)	17 (6)	1 (0.4)	–	–	1 (0.4)	–	56 (21)
Italy	167	5 (3)	52 (31)	58 (35)	20 (12)	6 (4)	6 (4)	–	1 (0.6)	–	–	19 (11)
Spain	296	8 (3)	110 (37)	89 (30)	65 (22)	5 (2)	6 (2)	–	1 (0.3)	–	–	12 (4)
Austria	81	14 (17)	20 (25)	21 (26)	5 (6)	5 (6)	1 (1)	–	–	–	–	15 (19)
Belgium	82	6 (7)	31 (38)	19 (23)	4 (5)	7 (9)	5 (6)	–	–	–	–	10 (12)
Portugal	68	6 (9)	21 (31)	8 (12)	9 (13)	4 (6)	9 (13)	–	–	–	–	11 (16)
Switzerland	44	5 (11)	23 (52)	11 (25)	1 (2)	3 (7)	–	–	–	–	–	1 (2)
Latin America	364	3 (0.8)	49 (13)	73 (20)	45 (12)	19 (5)	51 (14)	5 (1)	3 (0.8)	10 (3)	16 (4)	90 (25)
Argentina	106	–	5 (5)	20 (19)	22 (21)	11 (10)	21 (20)	3 (3)	2 (2)	3 (3)	7 (7)	12 (11)
Brazil	159	–	28 (18)	34 (21)	18 (11)	2 (1)	17 (11)	2 (1)	–	1 (0.6)	4 (3)	53 (33)
Mexico	41	1 (2)	10 (24)	13 (32)	4 (10)	2 (5)	3 (7)	–	–	2 (5)	–	6 (15)
Venezuela	58	2 (3)	6 (10)	6 (10)	1 (2)	4 (7)	10 (17)	–	1 (2)	4 (7)	5 (9)	19 (33)
Asia	109	11 (10)	75 (69)	13 (12)	–	–	3 (3)	–	–	–	–	7 (6)
China	74	11 (15)	50 (68)	4 (5)	–	–	3 (4)	–	–	–	–	6 (8)
Taiwan	35	–	25 (71)	9 (26)	–	–	–	–	–	–	–	1 (3)
2010 survey												
Europe	1679	94 (6)	696 (41)	479 (29)	115 (7)	74 (4)	53 (3)	2 (0.1)	8 (0.5)	10 (0.6)	8 (0.5)	140 (8)
France	352	4 (1)	63 (18)	156 (44)	33 (9)	39 (11)	19 (5)	2 (0.6)	7 (2)	4 (1)	7 (2)	18 (5)
Germany	283	35 (12)	141 (50)	61 (22)	7 (2)	3 (1)	–	–	–	–	–	36 (13)
Italy	297	13 (4)	135 (45)	70 (24)	41 (14)	4 (1)	16 (5)	–	–	–	–	18 (6)
Spain	320	19 (6)	194 (61)	57 (18)	18 (6)	9 (3)	8 (3)	–	1 (0.3)	–	–	14 (4)
Austria	118	7 (6)	51 (43)	37 (31)	1 (0.8)	2 (2)	4 (3)	–	–	–	–	16 (14)
Belgium	133	3 (2)	67 (50)	41 (31)	5 (4)	7 (5)	–	–	–	4 (3)	–	6 (5)
Portugal	111	1 (0.9)	20 (18)	41 (37)	4 (4)	5 (5)	6 (5)	–	–	2 (2)	1 (0.9)	31 (28)
Switzerland	65	12 (18)	25 (38)	16 (25)	6 (9)	5 (8)	–	–	–	–	–	1 (2)
Latin America	679	17 (3)	130 (19)	155 (23)	62 (9)	51 (8)	131 (19)	3 (0.4)	4 (0.6)	15 (2)	22 (3)	89 (13)
Argentina	137	–	19 (14)	24 (18)	11 (8)	18 (13)	28 (20)	2 (1)	1 (0.7)	9 (7)	11 (8)	14 (10)
Brazil	280	12 (4)	67 (24)	65 (23)	40 (14)	11 (4)	25 (9)	–	1 (0.4)	3 (1)	1 (0.4)	55 (20)
Mexico	132	5 (4)	34 (26)	45 (34)	9 (7)	16 (12)	17 (13)	–	1 (0.8)	–	1 (0.8)	4 (3)
Venezuela	130	–	10 (8)	21 (16)	2 (2)	6 (5)	61 (47)	1 (0.8)	1 (0.8)	3 (2)	9 (7)	16 (12)
Asia	261	28 (11)	148 (57)	67 (26)	2 (0.8)	–	2 (0.8)	–	–	–	–	14 (5)
China	121	28 (23)	57 (47)	18 (15)	2 (2)	–	2 (2)	–	–	–	–	14 (12)
Taiwan	140	–	91 (65)	49 (35)	–	–	–	–	–	–	–	–

NK not known

had risen to 1,775 of 3,740 patients (47%) in 2009 and 2,619 of 3,820 surveyed patients (69%) in 2010. The frequency of testing, although low generally in 2008, was highest in the Asian group (5% of patients), and in the European region in 2009 (62%) and 2010 (78%), but clearly increased overall and in each region, in each year, from 2008 to 2010 ($p<0.0001$ for each comparison: Fig. 1). The fraction of patients whose tumors were tested for tumor *KRAS* mutation status as a percentage of all included patients and *KRAS* test outcomes are summarized according to region and line of therapy in Table 3 and according to region and country in Table 4. Given the small number of tests recorded, full data are not presented for 2008. Where a test had been requested, tumor *KRAS* mutation status was available at the time of the survey in 2009 and 2010 for 96% and 95% of all patients, respectively.

Timing and turnaround time of *KRAS* testing

In the 2010 survey, 73% (326 of 448), 63% (160 of 256), and 20% (28 of 139) of participating physicians in Europe, Latin America and Asia, respectively, reported that they would routinely request a tumor *KRAS* mutation test at the time of diagnosis of metastatic disease. Examination of the patient records revealed that 40%, 27%, and 12% of patients with mCRC, respectively, were actually recorded as having received a *KRAS* test as part of the physician's normal diagnostic routine.

Where a *KRAS* test had been carried out, the number of days to obtain the result was recorded for each included patient. These were collated and are presented on a regional and country basis for 2009 and 2010 (Fig. 2 and Table 5). In 2009, where *KRAS* test results were available, these were obtained within 15 days for 70%, 46% and 97% of tested

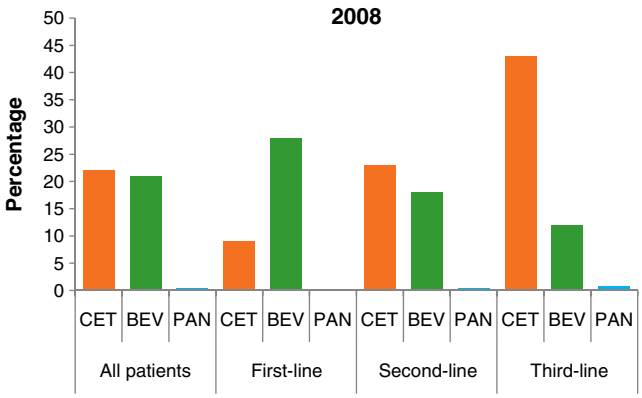


Fig. 3 Survey data from 2008 showing the percentage of patients in each line of therapy (and overall) who were receiving a particular monoclonal antibody as a component of their treatment regimen. *CET* cetuximab, *BEV* bevacizumab, *PAN* panitumumab

Fig. 4 Survey data from 2009 and 2010 showing the percentage of patients in each line of therapy (and overall), according to their *KRAS* test status and outcome, who were receiving a particular monoclonal antibody as a component of their treatment regimen. *CET* cetuximab, *BEV* bevacizumab, *PAN* panitumumab

patients respectively in the European, Latin American and Asian regions with median times of 14, 20 and 7 days. Although the proportion of patients tested had increased by 2010 in each region, the fraction of test results available within 15 days was marginally increased in each case to 82%, 51% and 98% and median times were 10, 15 and 7 days, respectively.

In 2009, at the time of the survey and considering all patients, *KRAS* mutation tests had been carried out on tumor tissue from a greater fraction of those receiving second- and third-line compared with first-line therapy ($p<0.0001$ for both comparisons). Similarly in the 2010 survey, although *KRAS* tumor mutation status had been examined for a higher proportion of patients undergoing first-line therapy (64%, compared with 41% in 2009) such testing had again been carried out for a greater proportion of patients receiving second- ($p=0.0024$) and third- ($p<0.0001$) compared with first-line treatment.

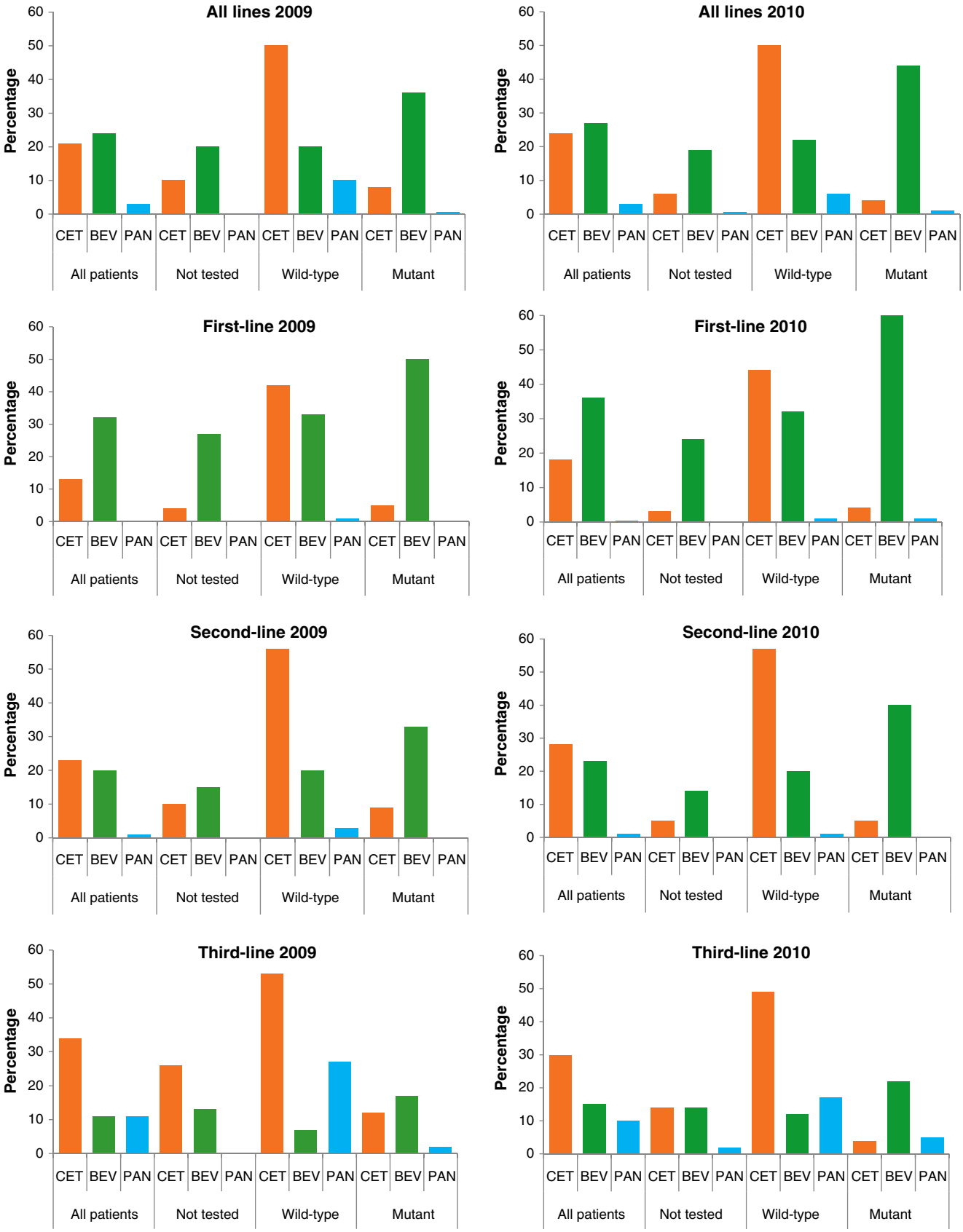
KRAS mutation status

Of 1,701 and 2,500 tumors typed for *KRAS* status in 2009 and 2010, 1,065 (63%) and 1,607 (64%) were deemed to be *KRAS* wild type, indicating an overall *KRAS* mutation rate of 37% and 36%, respectively for 2009 and 2010. In both 2009 and 2010, significantly fewer tested patients in the Asian region had *KRAS* mutations identified in their tumors compared with those in the European and Latin American regions (Table 3: respectively, 2009: 24% versus 38%, $p=0.0036$ and 24% versus 39%, $p=0.0052$; 2010: 22% versus 36%, $p<0.0001$. and 22% versus 40%, $p<0.0001$).

For the combined all-countries population of both 2009 and 2010, the frequency of tumor *KRAS* mutations was also significantly lower in those patients receiving third-line compared with first-line therapy (2009: 31% versus 41%, $p=0.0009$; 2010: 30% versus 40%, $p<0.0001$). On a regional basis, in both years, this effect was most clearly demonstrated in the European patient group (2009: 30% versus 42%, $p=0.0002$; 2010: 30% versus 41%, $p=0.0003$) and was least apparent for those in the Latin American region (Table 3).

Use of therapeutic monoclonal antibodies in treatment regimens

Whether the patient's current treatment regimen included a therapeutic monoclonal antibody was also recorded in each year of the survey. As only 3% of patients received a *KRAS*


All lines 2009
All lines 2010
First-line 2009
First-line 2010
Second-line 2009
Second-line 2010
Third-line 2009
Third-line 2010
Percentage
0
10
20
30
40
50
60
CET
BEV
PAN
All patients
Not tested
Wild-type
Mutant

test in 2008, the data for this year are presented for all patients, regardless of *KRAS* mutation testing or outcome (Fig. 3). In 2009 and 2010, with increasing appreciation of the significance of *KRAS* status as a predictive factor for EGFR-targeting therapies and the consequent increase in the frequency of testing, the use of therapeutic monoclonal antibodies has been cross-referenced for each patient according to treatment line and whether their tumor had been tested for *KRAS* status and if so, according to whether the tumor was found to be *KRAS* wild-type or *KRAS* mutant (Fig. 4).

In the 2008 survey, 1,637 of 3,819 patients (43%) were receiving a targeted agent as part of their current treatment regimen. This was cetuximab in 22% of patients, bevacizumab in 21% and panitumumab in 0.4% of cases. Reflecting the existing regulatory approval at the time of the survey, cetuximab was used predominantly in the second- and third-line treatment settings (23% and 43% of patients) and was administered to only 9% of patients receiving first-line therapy. In contrast, bevacizumab was administered more frequently in the first-line compared with second- and third-line settings (28% compared with 18% and 12% of patients, respectively).

In the 2009 survey, targeted agent use was reported for 48% of patients overall, with 21% receiving cetuximab, 24% receiving bevacizumab and 3% receiving panitumumab (Fig. 4). In the 1957 patients (52%) whose tumors were not tested for *KRAS* status, bevacizumab was administered most commonly in the first- and second-line settings (27% and 15% of not-tested patients), with cetuximab administered most commonly in third-line treatment (26% of not-tested patients). With the more widespread testing of tumors in 2009, significant differences were apparent in the use of targeted agents in those with *KRAS* wild-type and *KRAS* mutant tumors. Cetuximab was the most commonly administered targeted agent in patients with *KRAS* wild-type disease, while bevacizumab was the most commonly administered targeted agent in patients with *KRAS* mutant tumors (Fig. 4). Panitumumab was most often used in the third-line treatment of patients with *KRAS* wild-type tumors, being administered to 27% of patients in this group, compared with the 53% of patients who received cetuximab and the 7% who received bevacizumab.

In the 2010 survey, *KRAS* testing was reported for 69% of patients and the use of targeted agents was described for 54% of patients overall. In the 1,201 patients (31%) whose tumors were not tested for *KRAS* status, bevacizumab was the most commonly administered targeted agent in all settings. As for patients in the 2009 survey, overall and in each treatment line, cetuximab was the most commonly administered targeted agent in patients with *KRAS* wild-type disease and bevacizumab was the most commonly administered targeted agent in patients with *KRAS* mutant tumors. In particular, cetuximab was included in the treatment regimens of 44%, 57% and 49% of patients with *KRAS* wild-type tumors undergoing respectively, first-, second- and third-line therapy (798/1,607 patients; 50% overall) and bevacizumab was administered to 60%, 40% and 22% of patients with *KRAS* mutant tumors (396/893 patients; 44% overall) in the same treatment settings (Fig. 4). As in the 2009 survey, the most frequent use of panitumumab was in the third-line treatment of patients with *KRAS* wild-type tumors, with 17% of this group receiving this agent.

Discussion

Molecular analyses of tumor tissues collected during the course of randomized clinical studies of panitumumab and cetuximab in mCRC provided strong evidence that the benefit from EGFR antibody therapy was limited to patients whose tumors were wild type at codons 12 and 13 of the *KRAS* gene [33–35]. Consideration of such data was reflected in the regulatory approval for panitumumab and cetuximab. In particular, in December 2007, the EMA granted a conditional marketing authorization for panitumumab as monotherapy for the treatment of patients with EGFR-expressing *KRAS* wild-type mCRC after failure of fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens. Furthermore, in July 2008, the EMA broadened the cetuximab label in relation to EGFR-expressing mCRC to include use in all treatment lines in combination with chemotherapy or as monotherapy in patients who had failed oxaliplatin- and irinotecan-based therapy and who were intolerant to irinotecan, with such use restricted to patients with *KRAS* wild-type tumors. In the case of chemotherapy plus the vascular endothelial growth factor antibody, bevacizumab, a similar retrospective analysis of material collected during a randomized phase III study did not demonstrate a restriction of activity in the first-line treatment of mCRC according to tumor *KRAS* mutation status [36]. Indeed, as yet, no predictive markers have been clinically validated for this agent [37].

Current European Society for Medical Oncology clinical guidelines now emphasize that the determination of the *KRAS* status of the tumor can be a key factor in the selection of the best combination regimen for the first-line treatment of patients with advanced CRC [37]. The three surveys described in the current manuscript therefore provide a comprehensive picture across a wide geographical distribution and different types of medical center of how this predictive molecular test for EGFR-targeting therapy has been adopted by healthcare providers and how it has impacted overall upon the choice of treatment regimens for patients with mCRC.

The questionnaire data collected at the beginning of 2008 show that *KRAS* testing was carried out in only a

small number of cases at this time (3%). However, in the survey carried out in 2009, the fraction of patients with mCRC receiving this test had increased dramatically to 47% and it increased substantially again in the following year, to 69%. These figures highlight the rapid and widespread adoption of this new predictive test by physicians actively involved in the routine treatment of patients with mCRC. The test can also be carried out quickly, as demonstrated in the Asian region where results were available within 15 days for 97% of tested patients in the 2010 survey. In Europe, where a higher percentage of patients were tested (78% versus 44% in Asia), the results for 82% of cases were available within 15 days. Testing was also found to be a very efficient process in that results were available at the time of survey for almost all tested patients in 2009 (96%) and 2010 (95%).

As might be expected given their more advanced progress along the treatment continuum, patients in later lines of therapy were significantly more likely to have had a tumor *KRAS* test carried out both in 2009 and 2010 than those currently receiving first-line therapy, although the proportion of patients receiving first-line therapy who had been tested clearly increased from 2009 (41%) to 2010 (64%). This later-line bias may in part reflect a perception that the logistical and practical requirements of *KRAS* testing might cause a delay in the administration of first-line therapy. However, the 2010 survey data confirm that such tests can be carried out rapidly and effectively as part of standard clinical practice. In the future, it might be anticipated that *KRAS* testing will routinely form part of the initial clinical work-up for patients with mCRC. This would have the advantage of providing the physician with the widest range of treatment options at the earliest possible stage and would avoid any delays that might accrue following a request for *KRAS* test data, for example, subsequent to treatment failure.

The surveys in 2009 and 2010 regarding the incidence of *KRAS* mutations provide two essentially independent data sets that can therefore be examined for corresponding significant trends. In this context, it is interesting to note that there was a significantly lower incidence of tumor mutations detected for patients in the Asian compared to European and Latin American groups in both years. The reason for this disparity is not clear. In addition, the frequency of patients with *KRAS* wild-type disease appeared to be higher in both years in patients receiving third-line compared with first-line therapy, both for the all-patient group and also for those in the European subgroup. This could reflect a measure of earlier-line treatment benefit, perhaps related to cetuximab administration, in patients with *KRAS* wild-type disease who were receiving third-line therapy at the time of survey or perhaps poor prognosis in patients with *KRAS* tumor mutations [38].

In summary, the described surveys highlight the rapid and widespread adoption of tumor *KRAS* testing by medical practitioners in routine practice, treating patients with mCRC. The use of this predictive molecular biomarker to inform the selection of treatment agents on an individual patient basis is now a standard procedure. This has lead to a stratification in which those with *KRAS* wild-type tumors are most likely to receive cetuximab and those with *KRAS* mutant tumors most likely to receive bevacizumab as the targeted agent component of treatment regimens.

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Conflict of interest statement F. Ciardiello, S. Tejpar, N. Normanno, T. Teague and B. Wohlschlegel reported that no funds were received in support of this study or that no benefits in any form have been or will be received from a commercial party related directly or indirectly to the subject of this manuscript. D. Mecadante reported that she has received or will receive benefits for personal or professional use from a commercial party related directly or indirectly to the subject of this manuscript. E. Van Cutsem reported that although he has not received and will not receive benefits for personal or professional use from a commercial party related directly or indirectly to the subject of this manuscript, benefits have been or will be received but are directed solely to a research fund, foundation, educational institution, or other non-profit organization with which he is associated.

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