Impact of biomarkers and primary tumor location on the metastatic colorectal cancer first-line treatment landscape in five European countries

George Kafatos^{*1} , Victoria Banks¹ , Peter Burdon² , David Neasham¹ , Kimberly A Lowe³ , Caroline Anger⁴, Fil Manuguid⁴ & Jörg Trojan⁵

¹Center for Observational Research, Amgen Ltd., 1 Uxbridge Business Park, Sanderson Road, Uxbridge, UB8 1DK, UK

²Medical Affairs, Amgen (Europe) GmbH, Suurstoffi 22, Postfach 94, Rotkreuz 6343, Switzerland

³Center for Observational Research, Amgen Inc., One Amgen Center Drive, MS D2262, Thousand Oaks, CA 91320, USA

⁴IQVIA Real-World & Analytics solutions, 210 Pentonville Road, London, N1 9JY, UK

⁵Medizinische Klinik 1, Universitätsklinikum Frankfurt, Goethe-Universität, Theodor-Stern-Kai 7, Frankfurt am Main, 60590, Germany

*Author for correspondence: Tel.: +44 189 552 5615; gkafatos@amgen.com

Background: Advances in therapies for patients with metastatic colorectal cancer (mCRC) and improved understanding of prognostic and predictive factors have impacted treatment decisions. **Materials & methods:** This study used a large oncology database to investigate patterns of monoclonal antibody (mAb) plus chemotherapy treatment in France, Germany, Italy, Spain and the UK in mCRC patients treated in first line in 2018. **Results:** Anti-EGFR mAbs were most often administered to patients with *RAS* wild-type mCRC and those with left-sided tumors, while anti-VEGF mAbs were preferred in *RAS* mutant and right-sided tumors. Adopted treatment strategies differed between countries, largely due to reimbursement. **Conclusion:** Biomarker status and primary tumor location steered treatment decisions in first line. Adopted treatment strategies differed between participating countries.

Lay abstract: Each patient's cancer is unique. For example, colon cancer on the left side is different from colon cancer on the right side. Colon cancer is different from cancer of the rectum. Cancers also have changes in their genes, which means some treatments should work, while others may not. Doctors can select among different medicines to find the drug that works best for each patient. We looked at patients with cancer of the colon or rectum that has spread to other organs. We tried to find out how doctors in Europe select drugs for their patients after performing tests called *RAS* or *BRAF*. We found that doctors make different choices in different countries.

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During the last decade, improvements in the treatment of metastatic colorectal cancer (mCRC) have increased median survival time for patients from 12 months to approximately 3 years [1,2]. Major drivers of this success were the development of an antiangiogenic agent, the VEGF inhibitor bevacizumab, of monoclonal antibodies (mAbs) that inhibit the EGFR namely panitumumab and cetuximab, and a better understanding of prognostic and predictive biomarkers and of the different molecular profiles of left- and right-sided tumors [3,4,5]. Further important factors were the improvements in the adoption of multi-disciplinary teams/tumor boards, new surgical techniques, or local ablative therapies [6].

Chemotherapy, anti-VEGF mAbs and anti-EGFR mAbs are now the mainstay of systemic mCRC therapy. In the first line following diagnosis of mCRC, treatment is planned according to patient fitness, resectability of the tumor and/or metastases, and the tumor's biomarker status [7]. The European Society for Medical Oncology (ESMO) recommends the use of biologicals (targeted agents) as first line of treatment for most patients unless

contraindicated [7]. According to EMA UK label, the anti-VEGF mAb bevacizumab should be used in combination with fluoropyrimidine-based chemotherapy [8]. Anti-EGFR mAbs should be used in combination with FOLFOX or FOLFIRI or as monotherapy in patients who have failed oxaliplatin- or irinotecan-based therapy, are intolerant of irinotecan (cetuximab) or have failed fluoropyrimidine-based therapy (panitumumab). Both are limited to patients with *RAS* wild-type tumors [9,10]. There is strong evidence that *BRAF* mutation is predictive for a lack of benefit from anti-EGFR mAbs, although some discussions remain [7,11]. Evidence from the BEACON trial suggests some benefit of adding anti-EGFR mAb-based therapy to *BRAF/MEK* inhibitors. Anti-EGFR mAbs are thought to block the anticipated escape mechanism resulting from *BRAF/MEK* inhibition [12].

Primary tumor location, a surrogate of the different molecular profiles of left- and right-sided tumors, although first described in 2001 [13], has gained increasing attention after a 2017 meta-analysis of its prognostic and predictive value in patients with *RAS* wild-type mCRC [14]. In this retrospective analysis, six randomized trials (CRYSTAL, FIRE-3, CALGB 80405, PRIME, PEAK and 20050181) were pooled, comparing chemotherapy plus anti-EGFR mAb therapy with chemotherapy or chemotherapy plus bevacizumab. A worse prognosis for overall survival, progression-free survival and objective response rate (ORR) was found for patients with right-sided primary tumors. Tumor side was also found to be predictive of treatment efficacy, with the greatest effect in patients with left-sided tumors receiving anti-EGFR mAb in combination with chemotherapy. Similar results were found when analyzing the anti-EGFR mAbs separately in the panitumumab trials PRIME [4,15,16] and PEAK [4,16,17] and the cetuximab trials CRYSTAL and FIRE-3 [18].

The present study aimed to capture the treatment patterns in the first line of therapy of mCRC patients actively treated in 2018 in real-world clinical practice in five European countries by tumor sidedness and biomarker status.

Materials & methods

Database

This was a retrospective analysis using a large oncology database (Oncology Dynamics™, IQVIA Ltd., London, the UK). The database was designed as a cross-sectional physician survey that collects anonymized individual-level information on drug-treated cancer patients in Europe (and other non-European countries) regardless of cancer type, disease stage and/or treatment [19,20,21,22,23,24,25,26]. The database has been described in detail elsewhere [27].

In brief, the database includes data from oncology centers in 10 countries (France, Germany, Italy, Spain and the UK, China, Japan, South Korea, Saudi Arabia and Mexico). It is designed as repeated quarterly cross-sectional cohorts and contains more than 167,000 cancer cases per year and over 35 cancer indications. The database captures patient information via a standardized electronic case report form entered by the treating physician from patients' health records. Stratified random sampling is used to select physicians to represent the distribution of specialties for each cancer indication and country. It is limited to patients treated with a cancer drug at the time of data collection and excludes patients solely treated with radiotherapy, surgery, supportive care or on active surveillance.

Objectives

The study objective was to describe the demographic and clinical characteristics, as well as treatment patterns, i.e. anti-EGFR mAbs, anti-VEGF mAbs and/or chemotherapy, for patients treated for mCRC in first line during 2018 by tumor sidedness and biomarker status.

Eligibility criteria

All mCRC patients from the participating countries recorded in the database who received active anti-cancer first-line treatment in the advanced/metastatic setting in 2018, fulfilled the International Classification of Diseases, Tenth Revision codes used to define the mCRC population, and had a diagnosis date between July 2013 and December 2018, were included. Patients with unknown *RAS* or *BRAF* status, or unknown primary tumor location were excluded. Clinical trial participants were excluded.

Demographic & clinical characteristics

Description of demographics included country, age, sex, treatment facility site type and subtype. Clinical characteristics included the quarter of diagnosis, the BMI, Eastern Cooperative Oncology Group performance status, stage at diagnosis, site of metastasis and location of primary tumor.

Figure 1. CONSORT flow diagram describing the primary tumor location and biomarker status of first line of therapy for metastatic colorectal cancer patients.

CONSORT: Consolidated standards of reporting trials; CRC: Colorectal cancer; mCRC: Metastatic colorectal cancer.

Left-sided tumors were defined as those originating in the splenic flexure, descending colon, sigmoid colon or rectum. Right-sided tumors were defined as those originating in the appendix, cecum, ascending colon or hepatic flexure as well as the transversum – between the hepatic and splenic flexure; this is in line with previous analyses, such as the meta-analysis of six trials mentioned above [14]. Tumor sidedness was determined by the treating physician. Where tumor sidedness was recorded as unknown by the physician, the International Classification of Diseases, Tenth Revision code, from which anatomy of tumor location could be determined, was used where available.

Statistical considerations

Frequencies and proportions were provided for mCRC patients within the selected cohorts with their corresponding 95% Binomial Exact CIs. SAS Software was used (SAS Enterprise Guide 7.1.; SAS Institute Inc., NC, USA).

Results

Patient & tumor characteristics

There were 4455 mCRC patients within the database who were actively drug treated in 2018. A full description of all 4455 patients can be found elsewhere [27]. Of these, 42.0% (n = 1871) were receiving their first advanced/metastatic line of therapy and thus eligible for the present analysis; their RAS and BRAF status as well as their primary tumor location were known. Of these 1871 patients, two were excluded from the analysis as they received therapy other than anti-EGFR mAbs plus chemotherapy, anti-VEGF mAbs plus chemotherapy or only chemotherapy (see

CONSORT [Consolidated Standards of Reporting Trials] flow diagram in [Figure 1](#)); 635 patients were from Italy, 337 from Germany, 318 each from France and the UK and 261 from Spain. The oncology center characteristics for the 1869 analyzed patients are provided in the supplemental material ([Supplementary Table 1](#)). Of patients, 60.8% (n = 1136) were male, 68.6% (n = 1282) were older than 60 years of age. Overall, 52.6% (n = 983) had *RAS* wild-type tumors and 6.5% (n = 122) had *BRAF* mutant tumors; 62.7% (n = 1172) had left-sided and 37.3% (n = 697) had right-sided or transverse primary tumors (summarized as right-sided). Left-sided tumors were *RAS* wild type in 55.8% of patients (n = 654). Of right-sided tumors, slightly fewer than half, 47.2% (n = 329), were *RAS* wild type. *BRAF* wild type status was found in 95.7% (n = 1122) of left-sided and 89.7% (n = 625) of right-sided tumors ([Table 1](#)). Further patient and tumor characteristics are listed in [Table 1](#).

Treatment landscape

Patients with *RAS* wild-type tumors were most commonly treated with anti-EGFR mAbs plus chemotherapy (62.6%; 95% CI: 59.5%, 65.6%). The remaining patients were treated equally with anti-VEGF mAbs plus chemotherapy (18.4%; 95% CI: 16.0%, 21.0%) or chemotherapy-only (19.0%; 95% CI: 16.6%, 21.6%). Patients with *RAS* mutant tumors were most commonly prescribed anti-VEGF mAbs plus chemotherapy (60.5%; 95% CI: 57.2%, 63.7%) followed by chemotherapy-only (38.1%; 95% CI: 34.9%, 41.4%). There were 12 patients (out of 886 *RAS* mutant patients) documented as receiving anti-EGFR mAbs plus chemotherapy (1.4%; 95% CI: 0.7%, 2.4%; [Table 2](#)).

Of the 983 *RAS* wild-type patients, 654 (66.5%) had left-sided tumors and 329 (33.4%) had right-sided tumors. For both groups of patients, the most common treatment was anti-EGFR mAbs plus chemotherapy (71.6%; 95% CI: 67.9%, 75.0% and 44.7%; 95% CI: 39.2%, 50.2%) for left- and right-sided tumors, respectively). Of the 886 *RAS* mutant patients, 518 (58.4%) had left-sided tumors and 368 (41.5%) had right-sided tumors. For both left- and right-sided *RAS* mutant tumors, the majority were treated with anti-VEGF mAbs plus chemotherapy (59.5%; 95% CI: 55.1%, 63.7%) for left-sided and 62.0%; 95% CI: 56.8%, 66.9% for right-sided) ([Table 2](#)).

Of the *RAS* wild-type patients, 108 (11.0%) were *BRAF* mutant. For tumors of both *RAS* and *BRAF* wild type status, the most common treatment was anti-EGFR mAbs plus chemotherapy (69.3%; 95% CI: 66.1%, 72.4%). For tumors of *RAS* wild type and *BRAF* mutant status the most common treatment were anti-VEGF mAbs plus chemotherapy (44.4%; 95% CI: 34.9%, 54.3%). Of the *RAS* mutant patients, 872 (98.4%) were *BRAF* wild type and 14 (1.6%) were documented as *BRAF* mutant. For *RAS* mutant and *BRAF* wild-type tumors the most common treatment were anti-VEGF mAbs (61.1%; 95% CI: 57.8%, 64.4%). In the rare case of patients who were reported as having both *RAS* and *BRAF* mutant tumor status (n = 14) the great majority was treated with chemotherapy only (78.6%; 95% CI: 49.2%, 95.3%) ([Table 3](#)).

When looking at the treatment landscape by country, there were differences regarding the adopted treatment strategies. In *RAS* wild-type mCRC patients, anti-VEGF mAbs plus chemotherapy were not prescribed in the UK as opposed to the other countries, in which anti-VEGF mAb-based combinations ranged from 15.2% in Spain to 25.6% in Italy. Patients with *RAS* mutant tumors also received anti-VEGF mAbs plus chemotherapy less frequently in the UK (5.1%; 95% CI: 2.2%, 9.8%) compared with other countries which ranged from 66.9% in France to 78.9% in Italy ([Supplementary Tables 2 & 3](#)).

Discussion

This study aimed to capture the treatment patterns in mCRC patients in real-world clinical practice in five European countries. There were large differences in treatment patterns by biomarker status and primary tumor location. *RAS* wild-type patients were mainly treated with anti-EGFR mAbs plus chemotherapy (62.6%; 95% CI: 59.5%, 65.6%) whereas *RAS* mutant patients were most commonly treated with anti-VEGF mAbs plus chemotherapy (60.5%; 95% CI: 57.2%, 63.7%). For *RAS* wild-type patients, anti-EGFR mAbs plus chemotherapy were more frequently prescribed in patients with left-sided compared with right-sided tumors (71.6%; 95% CI: 67.9%, 75.0% vs 44.7%; 95% CI: 39.2%, 50.2%, respectively). In *RAS* and *BRAF* wild-type patients, the most common treatment was anti-EGFR mAb plus chemotherapy (69.3%; 95% CI: 66.1%, 72.4%). *RAS* wild-type/*BRAF* mutant patients preferably received anti-VEGF mAbs (44.4%; 95% CI: 34.9%, 54.3%). For *RAS* mutant/*BRAF* wild-type patients, anti-VEGF mAbs plus chemotherapy was most commonly prescribed (61.1%; 95% CI: 57.8%, 64.4%).

Studies with a broad focus evaluating the patterns of mCRC treatment, especially in first line, are rare; the authors are not aware of any studies using a similarly broad research angle as theirs. The predecessor of the database that was used in the present study (Oncology Analyzer™), was previously used to evaluate treatment patterns in

Table 1. Patient demographics and disease characteristics.

Parameters, n (%)	Left-sided tumors (n = 1172)	Right-sided tumors [†] (n = 697)	Overall (n = 1869)
Sex			
– Female	445 (38.0)	288 (41.3)	733 (39.2)
– Male	727 (62.0)	409 (58.7)	1136 (60.8)
Age group at current line of therapy			
– <16	–	–	–
– 16–50	102 (8.7)	73 (10.5)	175 (9.4)
– 51–60	286 (24.4)	126 (18.1)	412 (22.0)
– 61–75	591 (50.4)	355 (50.9)	946 (50.6)
– ≥76	193 (16.5)	143 (20.5)	336 (18.0)
ECOG status at current line of therapy			
– 0	390 (33.3)	219 (31.4)	609 (32.6)
– 1	649 (55.4)	408 (58.5)	1057 (56.6)
– 2	120 (10.2)	60 (8.6)	180 (9.6)
– 3	3 (0.3)	6 (0.9)	9 (0.5)
– 4	1 (0.1)	1 (0.1)	2 (0.1)
– Unknown	9 (0.8)	3 (0.4)	12 (0.6)
Stage at diagnosis			
– Stage I	10 (0.9)	4 (0.6)	14 (0.7)
– Stage II	61 (5.2)	29 (4.2)	90 (4.8)
– Stage III	156 (13.3)	84 (12.1)	240 (12.8)
– Stage IV	905 (77.2)	558 (80.1)	1463 (78.3)
– Unknown	40 (3.4)	22 (3.2)	62 (3.3)
Primary tumor location			
– Left-sided	1172 (100.0)	–	1172 (62.7)
– Right-sided	–	593 (85.1)	593 (31.7)
– Transverse	–	104 (14.9)	104 (5.6)
RAS status			
– Wild type	654 (55.8)	329 (47.2)	983 (52.6)
– Mutant	518 (44.2)	368 (52.8)	886 (47.4)
BRAF status			
– Wild type	1122 (95.7)	625 (89.7)	1747 (93.5)
– Mutant	50 (4.3)	72 (10.3)	122 (6.5)
Site of metastasis			
– Liver & lung combination	281 (24.0)	164 (23.5)	445 (23.8)
– Liver only	343 (29.3)	193 (27.7)	536 (28.7)
– Liver with other combination	303 (25.9)	171 (24.5)	474 (25.4)
– Lung only	63 (5.4)	31 (4.4)	94 (5.0)
– Lung with other combination	59 (5.0)	26 (3.7)	85 (4.5)
– Other	123 (10.5)	112 (16.1)	235 (12.6)
Pre-existing comorbidities			
– No	541 (46.2)	334 (47.9)	875 (46.8)
– Yes	631 (53.8)	363 (52.1)	994 (53.2)
Type of comorbidities			
– Auto-immune disease	15 (1.3)	4 (0.6)	19 (1.0)
– Bone disease	12 (1.0)	10 (1.4)	22 (1.2)
– Cardiovascular	215 (18.3)	119 (17.1)	334 (17.9)
– Gastrointestinal	29 (2.5)	12 (1.7)	41 (2.2)

[†]Right-sided tumors include tumors of the transverse colon.

CRC: Colorectal cancer; ECOG: Eastern cooperative oncology group; NA: Not available.

Table 1. Patient demographics and disease characteristics (cont.).

Parameters, n (%)	Left-sided tumors (n = 1172)	Right-sided tumors [†] (n = 697)	Overall (n = 1869)
– Infection	5 (0.4)	1 (0.1)	6 (0.3)
– Metabolic	224 (19.1)	134 (19.2)	358 (19.2)
– Neurological	36 (3.1)	21 (3.0)	57 (3.0)
– Renal	41 (3.5)	34 (4.9)	75 (4.0)
– Respiratory	155 (13.2)	97 (13.9)	252 (13.5)
– Other	223 (19.0)	114 (16.4)	337 (18.0)
– None	513 (43.8)	309 (44.3)	822 (44.0)
– NA	28 (2.4)	25 (3.6)	53 (2.8)
CRC-related surgery			
– No surgery	548 (46.8)	308 (44.2)	856 (45.8)
– Surgery	624 (53.2)	389 (55.8)	1013 (54.2)

[†]Right-sided tumors include tumors of the transverse colon.
CRC: Colorectal cancer; ECOG: Eastern cooperative oncology group; NA: Not available.

Table 2. Treatments received overall and by *RAS* mutation status and primary tumor location, n (%) (95% CI).

Treatment	<i>RAS</i> wild type			<i>RAS</i> mutant		
	Left-sided	Right-sided	Total	Left-sided	Right-sided	Total
Anti-EGFR mAbs	468 (71.6) [67.9, 75.0]	147 (44.7) [39.2, 50.2]	615 (62.6) [59.5, 65.6]	11 (2.1) [1, 3.8]	1 (0.3) [0.0, 1.5]	12 (1.4) [0.7, 2.4]
Anti-VEGF mAbs	76 (11.6) [9.3, 14.3]	105 (31.9) [26.9, 37.3]	181 (18.4) [16.0, 21.0]	308 (59.5) [55.1, 63.7]	228 (62.0) [56.8, 66.9]	536 (60.5) [57.2, 63.7]
Chemo only	110 (16.8) [14.0, 19.9]	77 (23.4) [18.9, 28.4]	187 (19.0) [16.6, 21.6]	199 (38.4) [34.2, 42.8]	139 (37.8) [32.8, 42.9]	338 (38.1) [34.9, 41.4]
Total	654 (100.0) [99.4, 100.0]	329 (100.0) [98.9, 100.0]	983 (100.0) [99.6, 100.0]	518 (100.0) [99.3, 100.0]	368 (100.0) [99.0, 100.0]	886 (100.0) [99.6, 100.0]

Chemo: Chemotherapy; mAbs: Monoclonal antibodies.

Table 3. Treatments received overall and by *RAS* mutation status and *BRAF* mutation status, n (%) (95% CI).

Treatment	<i>RAS</i> wild type			<i>RAS</i> mutant		
	<i>BRAF</i> wild type	<i>BRAF</i> mutant	Total	<i>BRAF</i> wild type	<i>BRAF</i> mutant	Total
Anti-EGFR mAbs	589 (69.3) [66.1, 72.4]	26 (24.1) [16.4, 33.3]	615 (62.6) [59.5, 65.6]	12 (1.4) [0.7, 2.4]	0 (0.0) [0.0, 23.2]	12 (1.4) [0.7, 2.4]
Anti-VEGF mAbs	133 (15.6) [13.3, 18.3]	48 (44.4) [34.9, 54.3]	181 (18.4) [16.0, 21.0]	533 (61.1) [57.8, 64.4]	3 (21.4) [4.7, 50.8]	536 (60.5) [57.2, 63.7]
Chemo only	153 (17.5) [15.0, 20.2]	34 (31.5) [22.9, 41.1]	187 (19.0) [16.6, 21.6]	327 (37.5) [34.3, 40.8]	11 (78.6) [49.2, 95.3]	338 (38.1) [34.9, 41.4]
Total	875 (100.0) [99.6, 100.0]	108 (100) [96.6, 100.0]	983 (100.0) [99.6, 100.0]	872 (100.0) [99.6, 100.0]	14 (100.0) [76.8, 100.0]	886 (100.0) [99.6, 100.0]

Chemo: Chemotherapy; mAbs: Monoclonal antibodies.

the USA, the EU (France, Germany, Italy, Spain), the UK and Japan using data from 2007 [21], and in France, Germany, Italy and Spain using a 2009 data snapshot [28]. In 2007, treatment combinations including targeted therapy (bevacizumab) accounted for a limited proportion of administered regimens in the first-line mCRC setting, with the highest uptake in France with <20%, followed by Italy and Germany with <10% [21]. By 2009, the proportion of bevacizumab-containing regimens had increased to approximately 40% in France, Germany and Italy, and 30% in Spain; cetuximab-containing regimens accounted for 7–14% [28]. Approved indications have changed substantially since these studies were conducted, generally allowing for refined use of these agents. The anti-EGFR mAbs labels changed several times over the last years, including changes in mandatory wild type status of *KRAS* to *RAS* and of allowed chemotherapy backbone (Figure 2). Panitumumab was initially approved as monotherapy, then in combination with FOLFOX in first line and with FOLFIRI in second-line; the combination with FOLFIRI

Figure 2. Selected European union label changes relating to the patient population eligible for anti-EGFR monoclonal antibody therapy.

[†]And intolerant to irinotecan.

[‡]FOLFOX4 subsequently revised to FOLFOX (first line) in 2012.

[§]For patients who have received first-line fluoropyrimidine-based chemotherapy (excluding irinotecan).

Therapeutic indications have been abbreviated; please see [9] (panitumumab) and [10] (cetuximab) for full details.

CTx: Chemotherapy; CTxR: Chemotherapy refractory; FOLFOX: Folinic acid, fluorouracil and oxaliplatin; FOLFIRI: Folinic acid, fluorouracil and irinotecan; IRI: Irinotecan; mAb: Monoclonal antibody; WT: Wild type.

in first line followed in 2015 [29]. Additionally, ESMO guidelines were continuously updated to incorporate new clinical evidence [7] and entailed considerable shifts in treatment practices.

The meta-analysis of six Phase III trials by Arnold *et al.* provided strong evidence about the prognostic and predictive value of primary tumor location, which are biologically different [5]. It was shown that the greatest effect was obtained in patients with left-sided tumors receiving anti-EGFR mAbs in combination with chemotherapy [14]. In the present study, 71.6% (95% CI: 67.9%, 75.0%) of patients with left-sided *RAS* wild-type tumors and 44.7% (95% CI: 39.2%, 50.2%) of patients with right-sided *RAS* wild-type tumors received anti-EGFR mAb-based therapy, using a chemotherapy backbone. In the UK, the great majority of *RAS* mutant patients were treated with chemotherapy only (93.6%; 95% CI: 88.6%, 96.9%) whereas in the other European countries most patients were treated with anti-VEGF mAbs plus chemotherapy (between 67.2 and 78.9% in Germany and Italy, respectively). In the UK, National Institute for Health and Care Excellence (NICE) does not recommend the anti-VEGF mAb bevacizumab in combination with FOLFOX or oxaliplatin plus capecitabine (CAPEOX) for the treatment of mCRC [32] and it was removed from the UK cancer drug fund in November 2016 [33]. Apart from the differences in reimbursement in the different countries, it needs to be highlighted that the scientific evidence supporting a benefit of bevacizumab in patients with *RAS* mutant tumors is yet unclear, as was shown by a recent systematic review and network meta-analysis of ten papers reporting six randomized-controlled trials [34]. This analysis found a statistically nonsignificant benefit in progression-free survival and no benefit in overall survival for patients with *RAS* mutant mCRC receiving bevacizumab plus chemotherapy versus those receiving chemotherapy alone [34]. Prospective randomized, controlled clinical trials enrolling solely *RAS* mutant patients have not been conducted with bevacizumab. Interestingly, 1.4% (95% CI: 0.7%, 2.4%) of patients with *RAS* mutant tumors were documented to have received anti-EGFR mAbs plus chemotherapy. Patients with *RAS* mutant or unknown status should not receive anti-EGFR mAbs and it thus seems likely that this number is an error in either documentation or treatment choice. The tumors of 14 patients were documented as having both, a *RAS* and a *BRAF* mutation. *RAS* and *BRAF* mutations are considered as mutually exclusive although some rare cases have been reported in the literature [35,36,37] and there is evidence that with next-generation sequencing (NGS) more such cases might be identified [38,39]. Clinical implications of such concomitant mutations are still undetermined.

The topic of primary tumor location as a surrogate for biologically different tumor entities was accepted on a broader scale after the publication of the large meta-analysis of six clinical trials conducted by Arnold *et al.* [14]. From that time onwards, extensive research was conducted to investigate the prognostic potential of primary tumor location on outcomes, although much of this research was retrospective. Although the 2016 ESMO recommendations could not yet take into consideration the primary tumor location as they predated the meta-analysis, the ESMO pan-Asian guidelines have been updated to include treatment recommendations including

consideration of left- versus right-sided primary tumor location [40]. The pan-Asian ESMO guidelines recommend that for patients with left-sided *RAS* wild-type disease, a cytotoxic doublet such as FOLFOX or FOLFIRI plus an anti-EGFR mAb should be the treatment of choice, whereas for those with right-sided *RAS* wild-type tumors, the cytotoxic triplet FOLFOXIRI plus bevacizumab should be or a cytotoxic doublet plus an anti-EGFR mAb can be, the treatment of choice [40].

There are some limitations to the present analysis. This study focused on describing the treatment patterns by biomarker status and tumor sidedness. However, there was less focus on the impact on clinical characteristics, such as resectability of the metastases or patient fitness of the choice of treatment. The database does not capture data on hospitalizations or survival. Observed country differences might be partly explained by differences in local treatment guidelines, physician prescribing behaviors, or reimbursement policies, some of which have been outlined above but no systematic analysis of the impact of these factors on treatment choice was conducted. A discussion of the database itself can be found elsewhere [27].

Conclusion

In clinical practice in the five participating European countries, *RAS* wild-type patients were mainly treated with anti-EGFR mAbs plus chemotherapy whereas *RAS* mutant patients were most commonly treated with anti-VEGF mAbs plus chemotherapy in all countries except for the UK, where they were more commonly treated with chemotherapy-only in the UK. In *RAS* wild-type patients, the presence of a *BRAF* mutation diversified the prescribed treatments compared with *BRAF* wild-type patients.

Future perspective

In the era of precision medicine, there are many biomarker-driven drugs that are under development, especially within the oncology therapeutic area. As these drugs are gradually being introduced, it is important to understand the impact of biomarker status in the physicians' treatment decision making.

Summary points

- Advances in therapies for patients with metastatic colorectal cancer (mCRC) and improved understanding of prognostic and predictive factors such as biomarkers or the recognition of the clinical impact of the biological differences between left- and right-sided primary tumors have impacted mCRC treatment patterns.
- The present study used a large international oncology database to investigate the treatment landscape of anti-VEGF monoclonal antibodies (mAbs) and anti-EGFR mAbs, both in combination with chemotherapy or chemotherapy alone in the first line of therapy of mCRC patients actively treated in 2018 in real-world clinical practice in five European countries (France, Germany, Italy, Spain and the UK) by tumor sidedness and biomarker status.
- Of the 1869 analyzed patients, *RAS* wild-type patients were mainly treated with anti-EGFR mAbs plus chemotherapy (62.6%; 95% CI: 59.5%, 65.6%) whereas *RAS* mutant patients were most commonly treated with anti-VEGF mAbs plus chemotherapy (60.5%; 95% CI: 57.2%, 63.7%).
- Of *RAS* wild-type patients with left-sided primary tumors, 71.6% (95% CI: 67.9%, 75.0%) received anti-EGFR mAbs plus chemotherapy, as did 44.7% (95% CI: 39.2%, 50.2%) of *RAS* wild-type patients with right-sided primary tumors.
- For *RAS* wild-type/*BRAF* mutant as well as *RAS* mutant/*BRAF* wild-type patients, the most common treatment was anti-VEGF mAbs plus chemotherapy with 44.4% (95% CI: 34.9%, 54.3%) and 61.1% (95% CI: 57.8%, 64.4%), respectively.
- There were differences between countries regarding the adopted treatment strategies with the UK generally prescribing less frequently anti-VEGF mAb plus chemotherapy compared with the other countries.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/suppl/10.2217/fon-2020-0976

Author contributions

All authors were involved in, and contributed to, the drafting and critical review of this manuscript.

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Ethical conduct of research

The Oncology Dynamics database (IQVIA Ltd.) used in this study is fully anonymized and complies with relevant regulations for protecting patient privacy.

Data sharing statement

The data that support the findings of this study are available from IQVIA Ltd, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of IQVIA Ltd.

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