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Gastrointestinal Cancer

Withholding the Introduction of Anti-Epidermal Growth Factor Receptor: Impact on Outcomes in *RAS* Wild-Type Metastatic Colorectal Tumors: A Multicenter AGEO Study (the WAIT or ACT Study)

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Metastatic colorectal cancer • RAS status • Anti-epidermal growth factor receptor • Bevacizumab

Abstract

Background. Patients with *RAS* wild-type (WT) nonresectable metastatic colorectal cancer (mCRC) may receive either bevacizumab or an anti-epidermal growth factor receptor (EGFR) combined with first-line, 5-fluorouracil-based chemotherapy. Without the *RAS* status information, the oncologist can either start chemotherapy with bevacizumab or wait for the introduction of the anti-EGFR. Our objective was to compare both strategies in a routine practice setting.

Materials and Methods. This multicenter, retrospective, propensity score–weighted study included patients with a *RAS* WT nonresectable mCRC, treated between 2013 and 2016 by a 5-FU-based chemotherapy, with either delayed anti-EGFR or immediate anti-vascular endothelial growth factor (VEGF). Primary criterion was overall survival (OS). Secondary criteria were progression-free survival (PFS) and objective response rate (ORR).

Results. A total of 262 patients (129 in the anti-VEGF group and 133 in the anti-EGFR group) were included. Patients receiving an anti-VEGF were more often men (68% vs. 56%), with more metastatic sites (>2 sites: 15% vs. 9%). The median delay to obtain the *RAS* status was 19 days (interquartile range: 13–26). Median OS was not significantly different in the two groups (29 vs. 30.5 months, $p = .299$), even after weighting on

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the propensity score (hazard ratio [HR] = 0.86, 95% confidence interval [CI], 0.69–1.08, p = .2024). The delayed introduction of anti-EGFR was associated with better median PFS (13.8 vs. 11.0 months, p = .0244), even after weighting on the propensity score (HR = 0.74, 95% CI, 0.61–0.90, p = .0024). ORR was significantly higher in the anti-EGFR group (66.7% vs. 45.6%, p = .0007).

Conclusion. Delayed introduction of anti-EGFR had no deleterious effect on OS, PFS, and ORR, compared with doublet chemotherapy with anti-VEGF. ***The Oncologist*** 2020;25:e266–e275

Implications for Practice: For *RAS/RAF* wild-type metastatic colorectal cancer, patients may receive 5-fluorouracil-based chemotherapy plus either bevacizumab or an anti-epidermal growth factor receptor (EGFR). In daily practice, the time to obtain the *RAS* status might be long enough to consider two options: to start the chemotherapy with bevacizumab, or to start without a targeted therapy and to add the anti-EGFR at reception of the *RAS* status. This study found no deleterious effect of the delayed introduction of an anti-EGFR on survival, compared with the introduction of an anti-vascular endothelial growth factor from cycle 1. It is possible to wait one or two cycles to introduce the anti-EGFR while waiting for *RAS* status.

Introduction

Colorectal cancer is the third most frequent cancer and the second most common cause of cancer-related mortality worldwide, with an estimated mortality rate of up to 880,000 deaths per year [1]. Based on the CALGB/SWOG 80405 and FIRE-3 phase III trials, guidelines in first-line *RAS/BRAF* wild-type (WT) nonresectable metastatic colorectal cancer (mCRC) recently proposed as main treatment option fluorouracil (5-FU)-based doublet chemotherapy with either an anti-vascular endothelial growth factor monoclonal antibody (anti-VEGF: bevacizumab) or an anti-epidermal growth factor receptor monoclonal antibody (anti-EGFR: cetuximab or panitumumab) [2–4]. The CALGB/SWOG 80405 trial [3] identified no differences in terms of median progression-free survival (PFS) or overall survival (OS) in patients receiving 5-FU-based doublet chemotherapy plus either bevacizumab or cetuximab.

More than half of mCRC harbor a *RAS* mutation (*KRAS* or *NRAS*). In 2008, the high predictive value of *KRAS* mutations in response to cetuximab was identified [5]. Those results were confirmed with extended mutations in *KRAS* and *NRAS* exons 2, 3, and 4, justifying the result of *RAS* status before the introduction of an anti-EGFR in first-line chemotherapy for *RAS* WT mCRC [6–8].

It has been highlighted that *KRAS* and *NRAS* results may be received with significant delays: the Flash-RAS study [9] reported that the median time from the request by physicians to results for a *KRAS* and *NRAS* status test in 2014 in France was 20 days.

While waiting for the *RAS* status, oncologists have two options: first, to not wait for *RAS* status and use doublet chemotherapy with bevacizumab; second, to initiate doublet chemotherapy without any monoclonal antibody, and to introduce subsequently the anti-EGFR when the WT *RAS* status is available. To our knowledge, no study has ever compared both strategies.

We aimed to evaluate the impact of both strategies on OS in a retrospective, multicenter study.

Materials and Methods

This observational, comparative, multicenter, retrospective study involved 28 centers (22 university hospitals, 4 cancer centers, and 2 general hospitals).

Patients

All consecutive patients with a nonresectable mCRC, treated with an anti-EGFR or anti-VEGF from January 1, 2013, to September 30, 2016, were screened by researching in chemotherapy prescription software. Exclusion criteria were as follows: a *KRAS*, *NRAS*, or *BRAF* mutated status; an incomplete *RAS* analysis (*KRAS* exon 2, 3, 4 and *NRAS* exon 2, 3, 4); a treatment without 5-FU-based doublet chemotherapy; bevacizumab introduction after cycle 1 or an anti-EGFR introduction at cycle 1 or after cycle 3; no measurable target lesion; evolving concomitant, progressive malignant tumor; a life expectancy of less than 3 months; an adjuvant chemotherapy received in the previous 6 months; a contraindication to an anti-VEGF or a surgery in a curative intent in the first 4 months. Patients included could receive doublet chemotherapy with 5-FU (or with tomudex in case of complete deficiency of dihydropyrimidine dehydrogenase) and oxaliplatin or irinotecan. The targeted therapy was an anti-VEGF (bevacizumab, aflibercept) started at first cycle or an anti-EGFR (cetuximab or panitumumab) started at cycle 2 or 3. Of note, we included aflibercept-treated patients from a phase II trial evaluating its efficacy in first line. Chemotherapy could be administered at reduced doses if any severe adverse event related to treatment occurred, and/or in frail patients, as routine clinical practice in each center. Body weight, performance status, and toxicities were recorded at each cycle or physician visit. Grades of adverse events were based on the Common Terminology Criteria for Adverse Events version 4.0 (http://ctep.cancer.gov).

The present study obtained the approval from the National Commission on Computer Technology and Freedom (*Commission Nationale de l'Informatique et des Libertés*; CNIL DR-2018-028), was in accordance with the Declaration of Helsinki, and was approved by our local ethics committee (*Comité Local d'Ethique des publications de l'hôpital Cochin*; CLEP AAA-2016-026083) according to French regulations. All data were collected from medical files and reported in an online Case Report Form.

Outcomes

The primary judgment criterion was median OS, defined as the time between the first cycle of chemotherapy and death. Patients alive at the time of the last assessment were censored. The secondary objectives were median PFS and objective response rate (ORR). PFS was defined as the time between the first cycle of chemotherapy and the first progression or death. Patients alive without any progression at the time of the last assessment were censored. ORR was

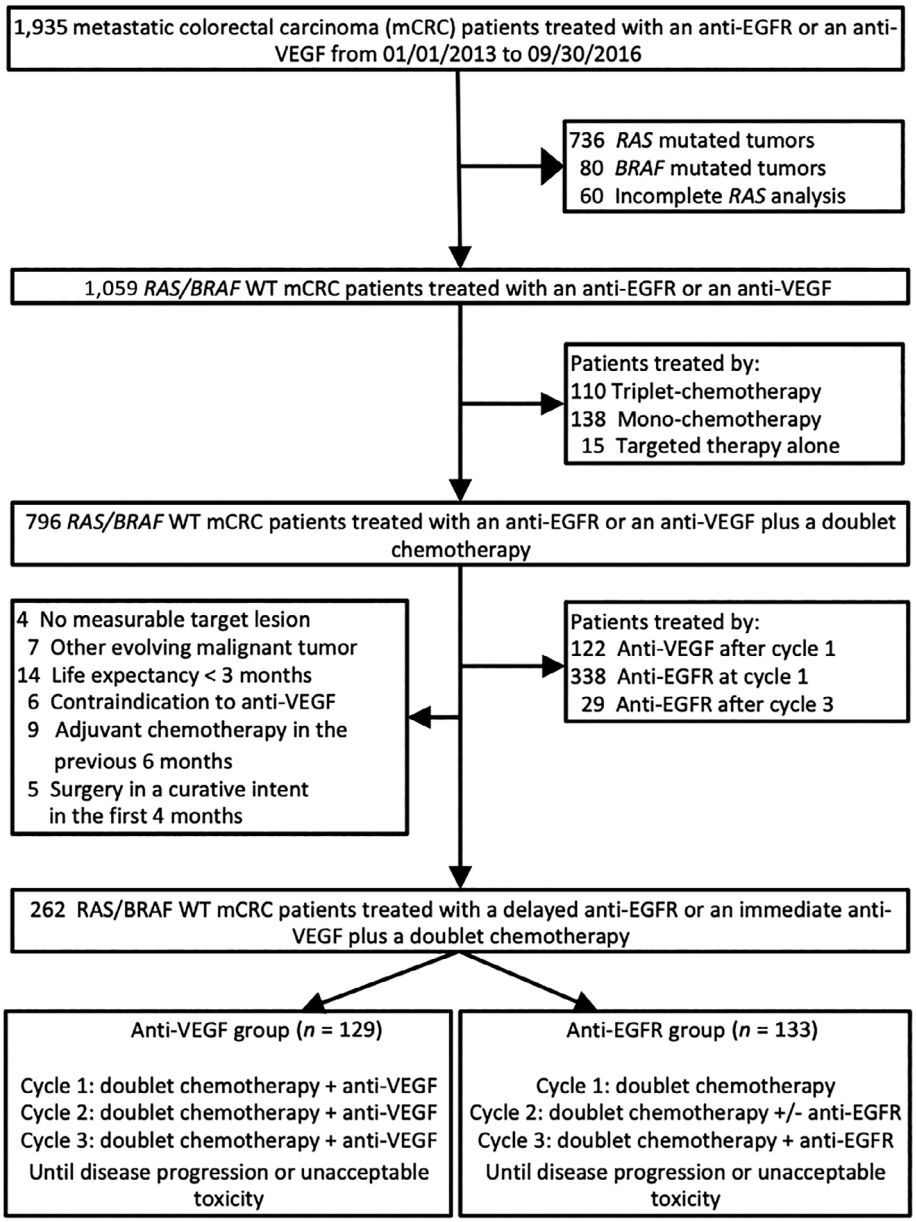

Figure 1. Flow chart.
Abbreviations: EGFR, epidermal growth factor receptor; mCRC, metastatic colorectal cancer; VEGF, vascular endothelial growth factor; WT, wild-type.

defined as the percentage of patients with a complete or partial response at first disease evaluation. Tumor evaluation was performed using computed tomography (CT) scan every four, six, or eight cycles of treatment or before if clinically indicated, according to RECIST version 1.1 [10]. In patients whose tumors were evaluated at the fourth and eighth cycles, the response at cycle 8 was considered for the ORR, in comparison with the baseline CT scan.

Statistical Analysis

Patients' demographic and disease characteristics and treatments were presented according to the targeted therapy strategy received. Median and interquartile range (IQR) and mean and SD were used to describe continuous variables and frequencies, and percentages were used to describe categorical variables. They were compared using the Wilcoxon test and chi-square or Fisher's *t* test when appropriate. Survival medians and their 95% confidence intervals (CIs) were estimated by the Kaplan-Meier method and compared with the log-rank test. Follow-up median estimations were assessed by the reverse Kaplan-Meier method.

Hazard ratios (HRs) with 95% CI were estimated with Cox proportional hazard regression. Variables with $p < .1$ in univariate models were then included in the multivariate analysis. Proportionality assumptions were graphically checked plotting the log (-log) survival.

An analysis with a propensity score approach was also used to limit bias due to potential heterogeneity in baseline characteristics between the two strategy groups. Variables associated with survival and unbalanced between groups

Table 1. Patient and treatment characteristics and treatments received in the anti-VEGF group and in the delayed anti-EGFR group

Characteristics	Anti-VEGF group (*n* = 129)	Anti-EGFR group (*n* = 133)	*p* value
Age, median (range), years	63.5 (57.1–73.6)	63.8 (55.1–71.8)	.476
Sex			.048
Men	88 (68.2)	75 (56.4)	
Women	41 (31.8)	58 (43.6)	
Tumor localization			.296
Right/transverse	21 (16.9)	29 (22.1)	
Left/rectum	103 (83.1)	102 (77.9)	
Primary tumor resected			.825
No	52 (40.9)	55 (42.3)	
Yes	75 (59.1)	75 (57.7)	
Previous treatment			.061
No	68 (53.1)	84 (64.6)	
Yes	60 (46.9)	46 (35.4)	
MSI status			.172
MSI	59 (89.4)	66 (93.0)	
MSS	7 (10.6)	5 (7.0)	
Grade			.538
Poorly differentiated	11 (12.4)	17 (18.3)	
Moderately differentiated	48 (53.9)	46 (49.5)	
Well differentiated	30 (33.7)	30 (32.2)	
Metastases delay			.134
Synchronous	83 (64.3)	97 (72.9)	
Metachronous	46 (35.7)	36 (27.1)	
Number of metastatic sites			.019
1	55 (42.6)	79 (59.8)	
≥2	74 (57.4)	53 (40.2)	
Metastatic sites			.047
Liver	61 (47.7)	46 (34.9)	
Liver only	31 (24.2)	49 (37.1)	
Liver not affected	36 (28.1)	37 (28.0)	
Resection of metastases			.255
Yes	10 (22.7)	21 (32.8)	
No	34 (77.3)	43 (67.2)	
Chemotherapy regimen			.049
Oxaliplatin-based chemotherapy, with:			
5-FU	76 (58.9)	95 (72.0)	
Capecitabine	1 (0.8)		
Tomudex	1 (0.8)		
Irinotecan-based chemotherapy, with:			
5-FU	50 (38.8)	37 (28.0)	
Capecitabine	1 (0.8)		
Targeted therapy			
Bevacizumab	119 (92)	—	
Aflibercept	10 (8)	—	
Cetuximab	—	55 (41)	
Panitumumab	—	78 (59)	

(continued)

Table 1. (continued)

Characteristics	Anti-VEGF group (*n* = 129)	Anti-EGFR group (*n* = 133)	*p* value
Number of cycles before targeted therapy			
0	129 (100)	—	
1	—	93 (69.9)	
2	—	40 (30.1)	

Values are expressed as *n* (%) or as median and range.
Abbreviations: —, not applicable; 5-FU, fluorouracil; EGFR, epidermal growth factor receptor; MSI, microsatellite instability; MSS, microsatellite stability; VEGF, vascular endothelial growth factor.

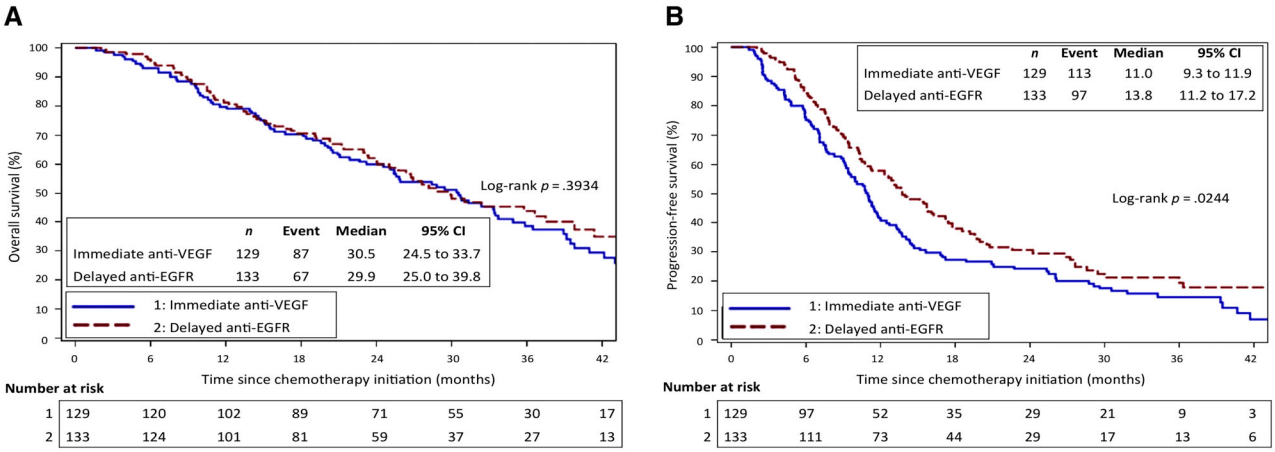

Figure 2. Kaplan-Meier estimates of survival among patients in the delayed anti-EGFR group or in the anti-VEGF group. **(A):** Progression-free survival. **(B):** Overall survival.
Abbreviations: CI, confidence interval; EGFR, epidermal growth factor receptor; VEGF, vascular endothelial growth factor.

were included in a multivariate logistic regression to estimate the probability to receive anti-EGFR and to construct the propensity score. Cox regression models were then weighted on the propensity score using the inverse probability of treatment weighting method (IPTW).

Association of the two groups and OS and PFS was investigated according to the sidedness of colorectal cancer, and a $p < .1$ for the interaction test was considered significant.

Analyses were conducted using SAS statistical software, version 9.33 (SAS Institute Inc., Cary, NC).

Results

Patients' Characteristics

A total of 1,935 patients were screened (Fig. 1). After applying the exclusion criteria previously described, 262 patients were finally included: 129 in the anti-VEGF group and 133 in the delayed anti-EGFR introduction group. Among the 500 patients with a *RAS* and *BRAF* WT mCRC treated with anti-EGFR, 68% (*n* = 338), 19% (*n* = 93), 8% (*n* = 40), and 6% (*n* = 29) had an anti-EGFR introduced at cycle 1, cycle 2, cycle 3, or after, respectively.

Patients in the anti-VEGF group were more frequently males (68% vs. 56%, *p* = .048) and had more metastatic sites (57% vs. 40%, *p* = .005; Table 1). In the anti-EGFR group, 41% (*n* = 55) of patients received cetuximab and 59% (*n* = 78) received panitumumab. In the anti-EGFR group, the use of oxaliplatin-based doublet chemotherapy was significantly higher than in the anti-VEGF group (72% vs. 60%, *p* = .049).

Delays for *RAS* Status

The median time to obtain *RAS* status was 19 days (IQR = 13–26), with a mean time to *RAS* status information of 21.3 days (SD = 17.1). The median time between the physician's request for *RAS* status and the receipt of the tumoral block by the molecular platform was 3 days (IQR = 0–11). The median time between receipt of the block and the result of *RAS* status was 11 days (IQR = 7–16). There was no significant difference between the two groups with regard to these timelines (*p* = .3993; supplemental online Table 1).

Propensity Score Analyses

Variables unbalanced between groups and significantly associated with survival in univariate Cox analyses were the number of metastatic sites and previous adjuvant treatment. These two parameters were included in a multivariate logistic regression (supplemental online Table 2) to construct the propensity score. The model exhibited acceptable discrimination capability, with an area under the curve equal to 0.6147 (supplemental online Fig. 1), and good calibration, with a *p* value for the Hosmer-Lemeshow goodness of fit test equal to .9953. No difference impacting survival was found between groups after weighting on the propensity score.

Overall Survival

In the overall population, the median follow-up was of 37.9 months (95% CI, 36.7–39.9). One hundred fifty-four

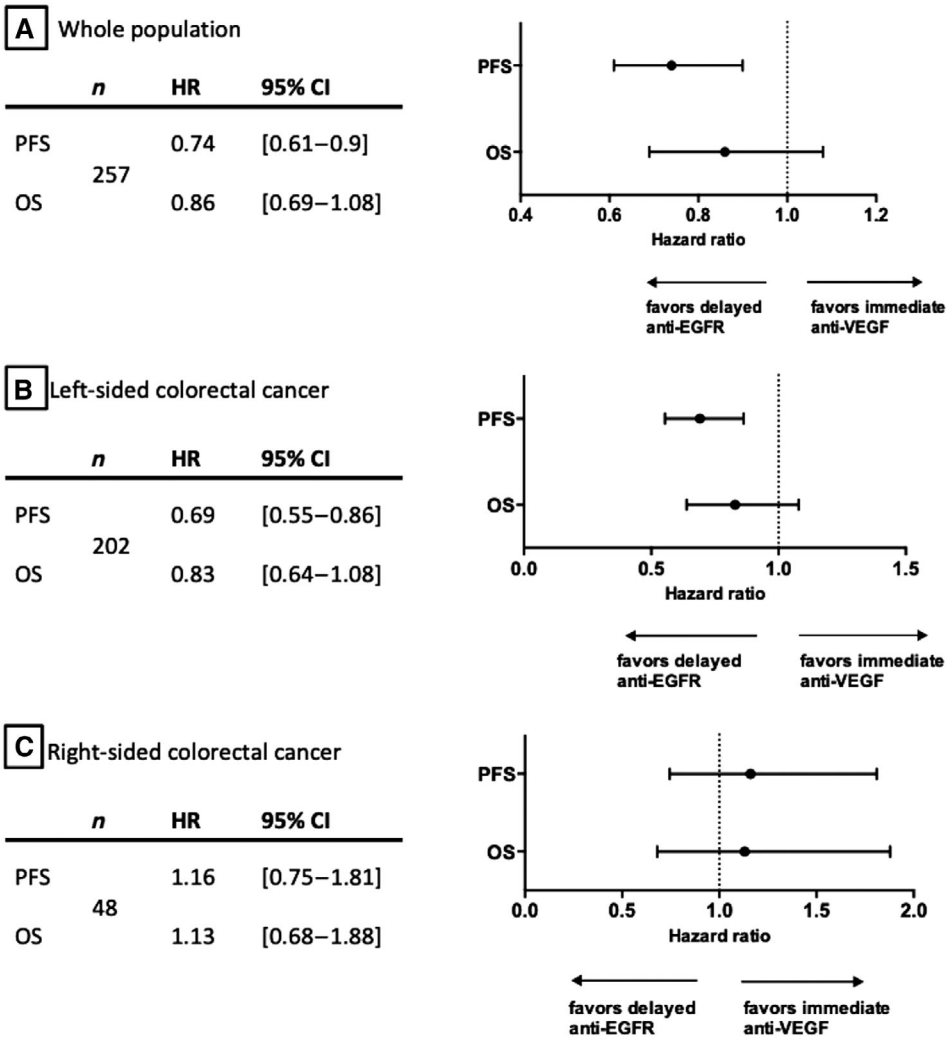

Figure 3. Forest plots showing hazard ratios for overall survival and progression-free survival, according to the sidedness of colorectal cancer. **(A):** Whole population. **(B):** Patients with left-sided colorectal cancer. **(C):** Patients with right-sided colorectal cancer. Data are weighted on the propensity score with inverse probability of treatment weighting.
Abbreviations: CI, confidence interval; EGFR, epidermal growth factor receptor; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; VEGF, vascular endothelial growth factor.

deaths were observed (59% of the whole cohort): 87 and 67 in the anti-VEGF and in the anti-EGFR group, respectively.

Median OS was not statistically different between the two groups: 30.5 months in the anti-VEGF group (95% CI, 24.5–33.7) versus 29.9 months in the anti-EGFR group (95% CI, 25.0–39.8), log-rank *p* value = .3934 (Fig. 2A).

After weighting on the propensity score, there was still no significant difference in OS between the two groups (HR = 0.86; 95% CI, 0.69–1.08, *p* = .2024; Fig. 3A).

In univariate Cox analysis, right-sided colorectal cancer, the absence of resection of the primary tumor, multiple metastatic sites, and the absence of previous adjuvant treatment were associated with a higher risk of death (supplemental online Table 3). No significant association between each targeted therapy and OS was found in either univariate analysis or multivariate analysis when adjusted on the tumor localization and on the resection of the primary tumor (HR = 0.83, 95% CI, 0.60–1.16, *p* = .2729; supplemental online Table 4).

Progression-Free Survival and Objective Response Rate

Two hundred two events (death or progression) were identified (80% of the entire cohort): 113 and 97 in the anti-VEGF and in the anti-EGFR groups, respectively. Median PFS was 11.0 months in the anti-VEGF group (95% CI, 9.3–11.9) and 13.8 months (95% CI, 11.2–17.2) in the anti-EGFR group (log-rank *p* = .0244; Fig. 2B). After weighting on the propensity score, HR remained significant in favor of anti-EGFR therapy: HR = 0.74, 95% CI, 0.61–0.90, *p* = .0024 (Fig. 3A). In univariate analysis, delayed anti-EGFR therapy was significantly associated with a lower risk of progression or death (HR = 0.73, 95% CI, 0.56–0.96, *p* = .0249; supplemental online Table 5) and was still associated when adjusted on the tumor localization and on the resection of the primary tumor (HR = 0.72, 95% CI, 0.54-0.95, *p* = .0215; supplemental online Table 6).

The ORR was significantly lower in the anti-VEGF group (*n* = 57, 45.6%) compared with the anti-EGFR group (*n* = 87, 66.7%; *p* = .0007).

Table 2. Adverse events

Adverse event	Grade	Anti-VEGF group (n = 129)	Anti-EGFR group (n = 133)	p value
Anemia	All grades	29 (22.5)	25 (18.8)	.4612
	1	29 (100)	20 (80)	
	2	4 (13.8)	7 (28)	
	3	0 (0)	1 (4)	
	4	0 (0)	0 (0)	
Neutropenia	All grades	28 (21.7)	22 (16.5)	.2876
	1	19 (67.9)	16 (72.7)	
	2	9 (32.1)	6 (27.3)	
	3	3 (10.7)	1 (4.6)	
	4	2 (7.1)	1 (4.6)	
Thrombopenia	All grades	11 (8.5)	18 (13.5)	.1966
	1	11 (100)	17 (94.4)	
	2	3 (27.3)	4 (22.2)	
	3	0 (0)	0 (0)	
	4	0 (0)	0 (0)	
Bleeding/hemorrhage	All grades	21 (16.3)	5 (3.8)	.0007
	1	18 (85.7)	5 (100)	
	2	2 (9.5)	0 (0)	
	3	0 (0)	0 (0)	
	4	1 (4.8)	0 (0)	
Diarrhea	All grades	71 (55.0)	63 (47.4)	.2143
	1	68 (95.8)	54 (85.7)	
	2	27 (38.0)	19 (30.2)	
	3	6 (8.5)	6 (9.5)	
	4	0 (0)	0 (0)	
Polyneuropathy	All grades	75 (58)	76 (57)	.8703
	1	71 (94.7)	75 (98.7)	
	2	31 (41.3)	31 (40.8)	
	3	4 (5.3)	6 (7.9)	
	4	0 (0)	1 (1.3)	
Skin reaction	All grades	32 (24.8)	94 (70.7)	<.0001
	1	27 (84.4)	87 (92.6)	
	2	9 (28.1)	59 (62.8)	
	3	1 (3.1)	12 (12.8)	
	4	0 (0)	0 (0)	

Values are expressed as n (%).
Abbreviations: EGFR, epidermal growth factor receptor; VEGF, vascular endothelial growth factor.

Left-Sided and Right-Sided Colorectal Cancer

For OS, no interaction between sidedness and group was found with the IPTW approach (p = .1759): HR = 0.83, 95% CI, 0.64–1.08 for left-sided colorectal cancer and HR = 1.13, 95% CI, 0.68–1.88 for right-sided colorectal cancer.

For PFS, a differential effect was found according to the sidedness (p = .0786). Patients with left-sided colorectal cancer seemed to benefit more from anti-EGFR (HR = 0.69, 95% CI, 0.55–0.86) than patients with right-sided colorectal cancer (HR = 1.16, 95% CI, 0.75–1.81; Fig. 3B, 3C).

Toxicities

Patients from the anti-VEGF group experienced a higher incidence of hemorrhagic events (p = .0007), whereas those from the anti-EGFR group experienced significantly more cutaneous adverse effects (p < .0001; Table 2).

Discussion

To our knowledge, this is the first study evaluating the strategy of delayed introduction of anti-EGFR compared with anti-VEGF from cycle 1, while waiting for the *RAS* status, in

first-line treatment of mCRC. We found no significant difference in terms of median OS between the two approaches. Delayed introduction of anti-EGFR was associated with a longer median PFS and a higher ORR, compared with doublet chemotherapy with anti-VEGF. These findings were not modified after weighting on the propensity score. These results strongly suggest that it is possible to introduce an anti-EGFR at cycle 2 or 3 while waiting for *RAS/BRAF* status.

The strategy of delayed introduction of anti-EGFR is frequent in clinical practice and was performed in 32% of the screened patients treated with an anti-EGFR in the present study. Lievre et al. identified a median delay from test request to receipt of the genotyping report of 20 days (IQR = 14.0–29.0). Our study is in line with this result, and therefore, the vast majority of patients in the anti-EGFR group received the anti-EGFR at cycle 2.

Our results are in line with those of the CALGB/SWOG 80405 study, which did not find any difference between anti-VEGF and anti-EGFR in terms of OS and PFS. In contrast, the phase II PEAK and phase III FIRE-3 studies found a significant benefit of the anti-EGFR on OS, compared with the anti-VEGF. The observed benefit on PFS in patients receiving anti-EGFR (13.8 months vs. 11.0 months, IPTW HR = 0.74 [95% CI, 0.61–0.90], p = .0024) is in line with the results of the phase II PEAK study, with similar median PFS values (13.0 months vs. 9.5 months, HR = 0.65, p = .03) [11]. However, there were no significant differences in PFS in FIRE-3 and CALGB/SWOG 80405 phase III studies. The benefit of anti-EGFR therapy on the ORR is consistent with the results of the post hoc analysis of the FIRE-3 trial [12]. Indeed, the ORR in the anti-EGFR group was 67% and 72% in our study and in the FIRE-3 study, respectively. Furthermore, a retrospective study compared in metastatic colorectal cancer *RAS* WT the introduction of the anti-EGFR at the first cycle versus the introduction at the second cycle versus the introduction at the third or fourth cycle, without any detrimental effect on OS and ORR of delayed addition of anti-EGFR agents [13]. Therefore, the strategy of a delayed introduction of an anti-EGFR appeared feasible and not deleterious compared with doublet chemotherapy with an anti-VEGF.

We found a significant difference in the number of metastatic sites between groups. The proportions of patients with two or more metastatic sites were, in the FIRE-3 study and in our study, 58% and 57% in the anti-VEGF group and 59% and 40% in the anti-EGFR group, respectively [4]. This discrepancy might be related to the physician's evaluation focused on the aggressiveness of the tumor based on the number of metastatic sites, with a will to initiate a targeted therapy rapidly (i.e., anti-VEGF) and not to wait for *RAS* status. This could also be related to the physician's choice for anti-EGFR for potentially resectable diseases with a conversion goal, a strategy based on the higher ORR observed in the post hoc analysis of the FIRE-3 study [12], leaving the anti-VEGF for patients with a heavier metastatic burden.

Recent data suggest a predictive effect of tumor location on the efficacy of anti-EGFR and anti-VEGF [14, 15]. In subgroups analyses, we identified a benefit on PFS of delayed anti-EGFR for left-sided mCRC. In contrast, we did not find a benefit of anti-VEGF on OS or PFS for right-sided mCRC. These results are in accordance with meta-analyses [14, 15], which found a benefit of the anti-EGFR for left-sided mCRC.

The median time to obtain *RAS* status, from *RAS* status test request to receipt of results, was in line with the results of the flash RAS study: 19 days versus 20 days, respectively [9]. These delays are similar to those found in 2011 and underline the difficulty of rapidly obtaining *RAS* status in routine clinical practice [16]. This is probably due to the need to send the samples to a molecular biology platform (sometimes located in another institution), and to the time required for *RAS* status determination itself. In addition, our data on time to obtain *RAS* status might be biased (i.e., shorter than in routine practice), because of the high number of university hospitals among centers participating in the present study (most of them having a molecular biology platform in the same institution and hence able to handle samples more rapidly). Delays to obtain *RAS* status set a real strategic issue, but the emergence of circulating tumor DNA (ctDNA) might help to address this issue. Indeed, the tissue-based methods have mean and median turnaround times of 13 days and 11 days, respectively, whereas plasma-based methods have both mean and median turnaround times of 2 days. According to Bachet et al. [17], there is a good concordance between *RAS* status in plasma and tumor tissue, with an accuracy up to 94.8% with next-generation sequencing for the patients with detectable ctDNA. Of note, the concordance rate varies according to studies and techniques from 78% to 93% [18, 19]. Another way to address this issue would be to test upfront all colorectal cancers, from the localized stage. *RAS* and *BRAF* are prognostic factors at a localized stage [20, 21]. Nevertheless, in the U.S., there are 145,600 new cases of colorectal cancer per year [22]. Testing *RAS* status for every new case of colorectal cancer would thus trigger an important medico-economic issue.

One of the strengths of our study is the diversity of the centers, reinforcing the representativeness of the study, with a picture of daily practice. Another strength of this study is the use of a propensity score, built to limit biases due to the retrospective nature of the study.

Otherwise, our study is limited by its retrospective design. Given the question and the retrospective design, the number of patients included is quite good, with well-balanced numbers of patients in the two groups, even if for a noninferiority design it would be underpowered. There are potentially important differences between the groups that may have confounded the results. There was a slightly unbalanced sex ratio with more women in the anti-EGFR group, without any explanation founded. We did not include the sex in our propensity score because no independent impact of sex on survival has been proved yet. In addition, patients in the anti-VEGF group had a higher number of metastatic sites at the initiation of first-line therapy. The use of a propensity score limited these differences between the groups, by weighting on the variables associated with survival and unbalanced characteristics between groups. We included 10 aflibercept-treated patients from a phase II trial, which may have been a selection bias. We did not compare the immediate introduction of the anti-EGFR to their delayed introduction, but Fiala et al. [13] compared immediate anti-EGFR to delayed anti-EGFR and suggested that there was

no difference between those two groups. Our study compared for the first time the strategy of a delayed introduction of an anti-EGFR to the recommended targeted therapy started at cycle 1. Another option would have been to compare delayed anti-EGFR plus doublet chemotherapy versus bevacizumab plus triplet chemotherapy. However, the strategy of triplet chemotherapy plus bevacizumab is currently less used than the doublet chemotherapy and is often used in selected patients. In addition, it has never been compared with doublet chemotherapy plus anti-EGFR. We did not include patients treated with an anti-EGFR introduced at C4 or more, to avoid the inclusion of patients with too low anti-EGFR exposure.

Conclusion

Our results suggest that the delayed introduction of an anti-EGFR (at cycle 2 or 3, while waiting for *RAS* status) does not impact median overall survival, compared with an anti-VEGF from cycle 1, in the first-line treatment for mCRC.

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Disclosures

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