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Panitumumab-based maintenance after oxaliplatin discontinuation in metastatic colorectal cancer: A retrospective analysis of two randomised trials

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Panitumumab is approved for *RAS* wild-type metastatic colorectal cancer and was evaluated in Phase III (PRIME, NCT00364013) and Phase II (PEAK, NCT00819780) first-line randomised studies. This retrospective analysis of these trials investigated efficacy and toxicity of panitumumab-based maintenance after oxaliplatin discontinuation in *RAS* wild-type patients. First-line regimens were FOLFOX4 ± panitumumab in PRIME and mFOLFOX6 plus panitumumab or mFOLFOX6 plus bevacizumab in PEAK. Outcomes included median progression-free survival (PFS) and overall survival (OS), from randomisation and oxaliplatin discontinuation, and toxicity. Overall, median duration of panitumumab plus 5-fluorouracil/leucovorin (5-FU/LV) maintenance was 21 (interquartile range: 11–41) weeks; that of 5-FU/LV ± bevacizumab maintenance was 16 (6–31) weeks. Median OS from randomisation was 40.2 (95% confidence interval: 30.3–50.4) and 39.1 (34.2–63.0) months for panitumumab plus 5-FU/LV maintenance and 24.1 (17.7–33.0) and 28.9 (21.0–32.0) months for 5-FU/LV ± bevacizumab maintenance in PRIME and PEAK, respectively. Median PFS from randomisation was 16.6 (11.3–23.6) and 15.4 (11.6–18.4) months for panitumumab plus 5-FU/LV maintenance and 12.6 (9.4–16.2) and 13.1 (9.5–16.6) months for 5-FU/LV ± bevacizumab maintenance in PRIME

Key words: epidermal growth factor receptor, maintenance, metastatic colorectal cancer, panitumumab, survival, toxicity

Abbreviations: 5-FU: 5-fluorouracil; CI: confidence interval; DpR: depth of response; ECOG: Eastern Cooperative Oncology Group; EGFR: epidermal growth factor receptor; ETS: early tumour shrinkage; FOLFOX4: fluorouracil, leucovorin and oxaliplatin; mFOLFOX: modified fluorouracil, leucovorin, and oxaliplatin; mCRC: metastatic colorectal cancer; OS: overall survival; PFS: progression-free survival; WT: wild type

Additional Supporting Information may be found in the online version of this article.

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and PEAK, respectively. From oxaliplatin discontinuation, median OS was 33.9 (24.7–42.8) and 33.5 (24.5–54.9) months for panitumumab plus 5-FU/LV maintenance and 16.4 (12.4–24.1) and 23.3 (15.7–26.3) months for 5-FU/LV ± bevacizumab maintenance in PRIME and PEAK, respectively; PFS was 11.7 (7.8–19.2) and 9.7 (5.8–14.8) months and 7.1 (5.6–10.2) and 7.0 (3.9–10.6) months, respectively. The most frequently reported adverse events were rash, fatigue and diarrhoea. Maintenance of panitumumab plus 5-FU/LV after oxaliplatin discontinuation was well tolerated and may be an acceptable treatment paradigm for patients demonstrating a good response to first-line treatment. Prospective studies are warranted.

What's new?

Panitumumab is an anti-EGFR antibody used in the treatment of *RAS* wild-type metastatic colorectal cancer. But is it useful for long-term therapy in these patients, especially after more toxic therapies like oxaliplatin are discontinued? In this retrospective analysis, the authors found that a maintenance regimen including panitumumab was well tolerated and may be associated with better outcomes than non-panitumumab strategies. Patients who received panitumumab-based maintenance therapy were also more likely to have had a good response to first-line treatment. The results from this study indicate that further, prospective studies are warranted.

Introduction

Panitumumab is a human anti-epidermal growth factor receptor (EGFR) monoclonal antibody indicated in the treatment of patients with *RAS* wild-type (WT) metastatic colorectal cancer (mCRC).[1,2] Panitumumab has been evaluated in several randomised clinical trials in mCRC, including the Phase III PRIME study (NCT00364013) and Phase II PEAK study (NCT00819780), both of which included extended *RAS* mutation testing (*KRAS* and *NRAS* exons 2, 3 and 4). Both studies assessed the use of panitumumab as part of oxaliplatin-containing first-line therapy.[3–6]

Clinical trial data show that continuation of first-line therapy until disease progression occurs only in a subpopulation of patients with mCRC, suggesting that systemic therapy is de-escalated in many patients before progression.[7,8] Considerations around maintenance therapy are of particular importance when drugs like oxaliplatin – associated with cumulative neurotoxicity – form part of adopted regimens. Accumulating toxicity can cause treatment discontinuation in responding patients and negatively impact quality of life. In light of such issues, 'stop-go' and/or maintenance strategies have been proposed.[9–11] Evaluation of such treatment paradigms is somewhat complicated by uncertainties around appropriate outcomes measures. Despite these challenges, 'stop-go' and maintenance treatment regimens have been shown to be effective (including with respect to overall survival [OS] and progression-free survival [PFS]), to have acceptable safety profiles,[9,11] and may also increase time to treatment failure.[12] With respect to biologics, data from Phase III maintenance trials are already available for bevacizumab-based maintenance regimens.[13,14]

There is currently little evidence available from prospective clinical trials focused on the role of anti-EGFR antibodies in the maintenance setting, although available data are encouraging.[15–17] To date, the role of panitumumab in maintenance therapy after discontinuation of oxaliplatin has not yet been properly investigated. The aim of this retrospective analysis of the PRIME and PEAK trials was to investigate the efficacy and toxicity of panitumumab-based maintenance treatment after discontinuation of oxaliplatin in a *RAS* WT subgroup. Preliminary results have been presented in abstract form.[18]

Materials and Methods

Study designs

As previously described,[3,6] the PRIME study was a randomised, open-label, Phase III clinical trial in which fluorouracil, leucovorin and oxaliplatin (FOLFOX4) was administered to patients with mCRC, either alone or in combination with panitumumab (6 mg/kg every 2 weeks), as first-line treatment. The PEAK study was a randomised, open-label, Phase II clinical trial in which modified fluorouracil, leucovorin and oxaliplatin (mFOLFOX6) was administered in combination with either panitumumab (6 mg/kg every 2 weeks) or bevacizumab (5 mg/kg every 2 weeks), as first-line treatment.[4,5] In both trials, it was foreseen that FOLFOX-based treatment would continue until progressive disease or unacceptable toxicity. Oxaliplatin discontinuation was recommended if Grade 3 neuropathy or other dose-limiting toxicity occurred. After discontinuation of oxaliplatin, the investigator could continue with existing 5-fluorouracil-based treatment (i.e., 5-FU/LV) in the absence or presence of panitumumab (or bevacizumab in the case of the PEAK study). Oxaliplatin could also be restarted during the follow-up period (i.e., 'stop-go' regimen) at the discretion of the investigator.

Populations

In brief, patients in the PRIME study were adults with previously untreated metastatic adenocarcinoma of the colon or

rectum, and an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2.[6] Patients in the PEAK study were adults with metastatic adenocarcinoma of the colon or rectum with unresectable metastatic disease, an ECOG performance status of 0 or 1, and WT *KRAS* exon 2 (codons 12 and 13). Patients in the PEAK study had not previously been treated with chemotherapy, anti-EGFR therapy or bevacizumab for mCRC.[5] Only patients with *RAS* WT mCRC were included in this retrospective analysis (i.e., patients without mutations in tumour *KRAS* or *NRAS* exons 2 [codons 12/13], 3 [codons 59/61] and 4 [codons 117/146]).

Analyses

Outcomes of first-line treatment were analysed in patients who subsequently received maintenance therapy after discontinuation of oxaliplatin and in patients who did not. Early tumour shrinkage (ETS) was calculated and defined as a ≥30% reduction in the sum of the longest diameters (mm) of measurable target lesions at week 8, compared with baseline. Depth of response (DpR) was calculated as the maximum percentage change from randomisation to nadir in patients who had tumour shrinkage. In patients with tumour growth or no change in tumour size, DpR was defined as the percentage change from randomisation to progression if the patient subsequently progressed, or as 'missing' if the patient did not progress. DpR was positive if there was tumour shrinkage, negative if there was tumour growth, and zero if there was no change. Overall response rates were evaluated per modified Response Evaluation Criteria in Solid Tumors (version 1.0). Kaplan-Meier estimates and 95% confidence intervals (CI) were calculated by treatment group for duration of response (for patients with an objective response on central [PRIME] or local [PEAK] review); duration of clinical benefit (for patients with an objective response or stable disease); and resection rates.

The following outcomes of maintenance therapy were calculated using the Kaplan-Meier method: median PFS (i.e., time from randomisation to disease progression or death); OS (i.e., time from randomisation until death); OS from oxaliplatin discontinuation (i.e., time from the start of maintenance treatment until death); and PFS from oxaliplatin discontinuation (i.e., time from the start of maintenance treatment until disease progression or death). Toxicity was also assessed via monitoring of adverse events occurring in first line and maintenance treatment or emerging during the maintenance treatment period (overall and Grade 3+).

Ethics approval and consent to participate

The PRIME and PEAK studies were conducted in accordance with the Declaration of Helsinki. Study protocols were approved by an independent ethics committee at each study centre. All patients provided informed consent.

Results

Patients, demographics and baseline characteristics

Of the 665 patients with *RAS* WT mCRC who participated in the two studies, 83 received panitumumab plus 5-FU/LV maintenance therapy and 71 received 5-FU/LV ± bevacizumab maintenance therapy. Five hundred and eleven patients did not receive maintenance therapy. Baseline demographics and disease characteristics, as well as details of first-line treatment, for each study are summarised in Table 1, and pooled data are provided in Supporting Information Table S1.

Outcomes during first-line treatment

First-line treatment outcomes are summarised in Table 2; pooled data are provided in Supporting Information Table S2. The median (range) number of oxaliplatin infusions that patients received during first-line treatment was 12 (2–31) and 11 (3–21) for panitumumab plus 5-FU/LV in PRIME and PEAK, respectively, 13 (5–41) for 5-FU/LV maintenance in PRIME and 12 (3–9) for 5-FU/LV plus bevacizumab maintenance in PEAK. Patients who received panitumumab plus 5-FU/LV maintenance therapy were more likely to have received ≥9 months of first-line treatment, to have experienced ETS and to have had higher rates of complete response and partial response than patients who received maintenance therapy with 5-FU/LV ± bevacizumab. These patients also had improved DpR, duration of response and duration of clinical benefit.

Outcomes during maintenance treatment

The median (interquartile range) duration of panitumumab plus 5-FU/LV maintenance therapy was 16 (8–41) weeks in PRIME and 28 (14–46) weeks in PEAK, while that of 5-FU/LV ± bevacizumab maintenance therapy was 15 (6–31) and 16 (9–30) weeks in PRIME and PEAK, respectively (Table 3). In patients who received panitumumab plus 5-FU/LV maintenance therapy, median OS from randomisation was longer compared to those receiving 5-FU/LV or 5-FU/LV plus bevacizumab maintenance therapy (40.2 [30.3–50.4] and 39.1 [34.2–63.0] months compared with 24.1 [17.7–33.0] and 28.9 [21.0–32.0] months in PRIME and PEAK, respectively (Table 3; Fig. 1). From oxaliplatin discontinuation, OS was 33.9 (24.7–42.8) and 33.5 (24.5–54.9) months in patients who received panitumumab plus 5-FU/LV maintenance therapy in PRIME and PEAK, respectively, and 16.4 (12.4–24.1) and 23.3 (15.7–26.3) months for those receiving 5-FU/LV ± bevacizumab maintenance therapy. In pooled analysis, median OS from randomisation was 40.2 (95% CI: 35.6–47.4) months for patients receiving panitumumab plus 5-FU/LV, compared with 25.3 (21.0–31.9) months in those receiving 5-FU/LV ± bevacizumab maintenance therapy and median OS from oxaliplatin discontinuation was 33.9 (28.4–41.3) and 18.8 (15.4–24.1) months, respectively (Supporting Information Table S3).

Median PFS from randomisation was 16.6 (11.3–23.6) and 15.4 (11.6–18.4) months in patients receiving panitumumab plus 5-FU/LV maintenance in PRIME and PEAK, respectively, compared with 12.6 (9.4–16.2) months in those receiving 5-FU/LV maintenance therapy in PRIME and 13.1 (9.5–16.6) months in those receiving 5-FU/LV plus bevacizumab maintenance therapy in PEAK (Table 3). Median PFS from oxaliplatin discontinuation was 11.7 (7.8–19.2) and 9.7 (5.8–14.8) months for patients receiving panitumumab plus 5-FU/LV maintenance in PRIME and PEAK, respectively, and 7.1 (5.6–10.2) and 7.0 (3.9–10.6) months for those receiving 5-FU/LV ± bevacizumab maintenance therapy (Table 3; Fig. 2). In pooled analysis, median PFS from randomisation was 15.4 (95% CI: 12.6–18.4) months for patients receiving panitumumab plus 5-FU/LV, compared with 13.1 (11.3–15.4) months in those receiving 5-FU/LV ± bevacizumab maintenance therapy and median PFS from oxaliplatin discontinuation was 10.2 (7.8–14.8) and 7.1 (6.6–9.2) months, respectively (Supporting Information Table S3). Overall, 22% of patients receiving panitumumab plus 5-FU/LV maintenance restarted oxaliplatin during the follow-up period, compared with 10% of those receiving 5-FU/LV ± bevacizumab maintenance (Supporting Information Table S3).

Toxicity

The adverse events that occurred most commonly during maintenance therapy were rash, fatigue and diarrhoea (Table 4). These events were also the most common adverse events to emerge during first-line therapy (Supporting Information Table S4). In the PRIME study, maintenance treatment-emergent dry skin was reported in 11.5% of patients receiving panitumumab plus 5-FU/LV maintenance therapy and 2.4% of patients receiving 5-FU/LV maintenance therapy. In the PEAK study, dry skin was reported in 19.4% of patients receiving panitumumab plus 5-FU/LV maintenance therapy and 0% of patients receiving 5-FU/LV + bevacizumab maintenance therapy (Table 4). The most frequent maintenance treatment-emergent Grade 3+ adverse events were paraesthesia (PRIME) and acne (PEAK) in the panitumumab plus 5-FU/LV maintenance groups, and peripheral neuropathy in the 5-FU/LV ± bevacizumab maintenance groups (Table 4).

Discussion

While the European Society for Medical Oncology mCRC guidelines recommend anti-EGFR monoclonal antibodies as a first-line treatment option,[2] little evidence is available on de-escalation strategies from EGFR-based combination regimens.

Table 1. Baseline demographics and disease characteristics

	PRIME			PEAK		
	Maintenance therapy			Maintenance therapy		
	Pmab + 5-FU/LV (*n* = 52)	5-FU/LV (*n* = 41)	None (*n* = 406)	Pmab + 5-FU/LV (*n* = 31)	5-FU/LV + bev (*n* = 30)	None (*n* = 105)
Median age (range), years	59 (41–79)	62 (24–78)	61 (27–82)	62 (23–75)	61 (39–79)	60 (39–82)
Male sex, *n* (%)	31 (60)	26 (63)	266 (66)	21 (68)	18 (60)	73 (70)
BRAF status, *n* (%)						
Wild-type	49 (94)	35 (85)	349 (86)	27 (87)	28 (93)	97 (92)
Mutant	3 (6)	4 (10)	46 (11)	4 (13)	2 (7)	8 (8)
Unknown	0 (0)	2 (5)	11 (3)	0 (0)	0 (0)	0 (0)
Tumour location, *n* (%)						
Left sided	40 (77)	27 (66)	261 (64)	21 (68)	18 (60)	68 (65)
Right sided	6 (12)	7 (17)	75 (18)	8 (26)	5 (17)	23 (22)
Unknown	6 (12)	7 (17)	70 (17)	2 (6)	7 (23)	14 (13)
Site of metastases, *n* (%)						
Liver + other	35 (67)	34 (83)	269 (66)	17 (55)	9 (30)	50 (48)
Liver only	12 (23)	4 (10)	73 (18)	10 (32)	10 (33)	24 (23)
Other only	5 (10)	3 (7)	64 (16)	4 (13)	11 (37)	31 (30)
ECOG performance status 0, *n* (%)	34 (65)	24 (59)	226 (56)	21 (68)	21 (70)	62 (59)
Stage IV disease at diagnosis,[1] *n* (%)	35 (67)	33 (80)	302 (74)	22 (71)	19 (63)	73 (70)
Prior adjuvant chemotherapy, *n* (%)	13 (25)	4 (10)	62 (15)	2 (6)	6 (20)	23 (22)

5-FU, 5-fluorouracil; bev, bevacizumab; ECOG, Eastern Cooperative Oncology Group; LV, leucovorin; Pmab, panitumumab.
[1]Presence of Stage IV disease at baseline was derived by taking date of metastases – date of primary diagnosis (allowing a 2-month window).

Table 2. Initial treatment and response to first-line therapy

	PRIME			PEAK		
	Maintenance therapy			Maintenance therapy		
	Pmab + 5-FU/LV (*n* = 52)	5-FU/LV (*n* = 41)	None (*n* = 406)	Pmab + 5-FU/LV (*n* = 31)	5-FU/LV + bev (*n* = 30)	None (*n* = 105)
Median number of oxaliplatin infusions before maintenance therapy (range)	12 (2–31)	13 (5–41)	11 (1–60)	11 (3–21)	12 (3–19)	10 (1–35)
First-line study drug exposure, *n* (%)						
‹3 months	0 (0)	0 (0)	83 (20)	0 (0)	0 (0)	27 (26)
≥3 to ‹6 months	5 (10)	3 (7)	131 (32)	1 (3)	2 (7)	37 (35)
≥6 to ‹9 months	8 (15)	13 (32)	93 (23)	5 (16)	8 (27)	23 (22)
≥9 months	39 (75)	25 (61)	99 (24)	25 (81)	20 (67)	18 (17)
Early tumour shrinkage ≥30%, *n* (%)	33 (63)	15 (37)	165 (41)	22 (71)	16 (53)	46 (44)
Best overall response, *n* (%)						
Complete response	1 (2)	0 (0)	1 (‹1)	3 (10)	1 (3)	4 (4)
Partial response	41 (79)	23 (56)	199 (49)	24 (77)	22 (73)	51 (49)
Stable disease	9 (17)	17 (41)	141 (35)	4 (13)	7 (23)	37 (35)
Progressive disease	1 (2)	1 (2)	47 (12)	0 (0)	0 (0)	5 (5)
Not available	0 (0)	0 (0)	18 (4)	0 (0)	0 (0)	8 (8)
Median duration of response (95% CI), months	14.8 (9.6–22.1)	14.3 (8.2–16.6)	9.3 (8.3–10.1)	13.2 (9.2–18.7)	10.3 (7.4–14.8)	9.2 (7.9–11.1)
Median duration of clinical benefit[1] (95% CI), months	14.8 (9.6–22.0)	11.1 (8.2–14.3)	8.6 (7.6–9.4)	13.7 (9.6–16.8)	11.2 (7.7–14.8)	8.8 (7.3–10.8)
Median depth of response (IQR), %	64 (48–78)	56 (43–68)	46 (22–68)	72 (50–85)	48 (39–61)	52 (29–86)
Resection, *n* (%)						
Any	7 (13)	4 (10)	53 (13)	1 (3)	4 (13)	18 (17)
Complete	5 (10)	4 (10)	36 (9)	0 (0)	2 (7)	14 (13)

5-FU, 5-fluorouracil; bev, bevacizumab; CI, confidence interval; IQR, interquartile range; LV, leucovorin; Pmab, panitumumab.
[1]Complete or partial response, or stable disease.

Our study, therefore, addresses a highly relevant clinical scenario, where evidence is currently limited.

One of the challenges in assessing the effects of maintenance therapy is the selection of appropriate outcome measures. Although of most interest to patients, the use of OS as an endpoint to evaluate the efficacy of maintenance treatment regimens is hampered by the need for extended follow-up and the potential impact of subsequent and prior first-line therapies.[11,14,19] It has therefore been argued that other endpoints are more relevant to the maintenance setting.[11,19,20] For example, some have argued that PFS[20] or time-to-failure-of-strategy[11,19] are more appropriate endpoints, while others caution that such endpoints can be difficult for patients to understand.[11] An analysis of over a 1,000 patients with mCRC found that time-to-failure-of-strategy and duration of disease control correlate well with OS.[21] In the present analysis, we assessed PFS and OS; time-to-failure-of-strategy data could not be derived from the studies. Additionally, toxicity outcomes were evaluated.

Literature evidence suggests that – based on randomised Phase II trials – anti-EGFR-based maintenance therapy is feasible in mCRC patients after oxaliplatin-based induction regimens. The MACRO-2 study evaluated maintenance cetuximab with or without mFOLFOX until progression in *KRAS* WT mCRC patients and reported non-inferiority for 9-month PFS rate (the primary endpoint) and OS.[15] Similarly, the COIN-B study evaluated first-line treatment with intermittent FOLFOX plus either intermittent or continuous cetuximab. Failure-free survival at 10 months was 50% in the intermittent group and 52% in the continuous group.[16]

Several other maintenance scenarios are currently under investigation, such as that studied in the SAPPHIRE trial, which compares continuation of panitumumab plus mFOLFOX6 with panitumumab plus 5-FU/LV maintenance[22] and recently reported 9-month PFS rates of 45% and 47%, respectively.[22,23] Other ongoing trials are expected to clarify the role of panitumumab plus 5-FU/LV in this setting: the VALENTINO non-inferiority trial,[24] which recently showed that panitumumab alone was inferior to panitumumab plus 5-FU/LV for unresectable *RAS* WT mCRC patients, after eight cycles of FOLFOX4 plus panitumumab induction treatment,[25] and the PanaMa superiority trial, which will compare panitumumab

Table 3. Treatment outcomes in patients receiving maintenance therapy after first-line treatment

	PRIME		PEAK	
	Pmab + 5-FU/LV maintenance (*n* = 52)	5-FU/LV maintenance (*n* = 41)	Pmab + 5-FU/LV maintenance (*n* = 31)	5-FU/LV + bev maintenance (*n* = 30)
Median duration of maintenance therapy (IQR), weeks	16 (8–41)	15 (6–31)	28 (14–46)	16 (9–30)
Restarted oxaliplatin during follow-up, *n* (%)	13 (25)	2 (5)	5 (16)	5 (17)
Median OS from randomisation (95% CI), months	40.2 (30.3–50.4)	24.1 (17.7–33.0)	39.1 (34.2–63.0)	28.9 (21.0–32.0)
Median PFS from randomisation (95% CI), months	16.6 (11.3–23.6)	12.6 (9.4–16.2)	15.4 (11.6–18.4)	13.1 (9.5–16.6)
Median OS from oxaliplatin discontinuation (95% CI), months	33.9 (24.7–42.8)	16.4 (12.4–24.1)	33.5 (24.5–54.9)	23.3 (15.7–26.3)
Median PFS from oxaliplatin discontinuation (95% CI), months	11.7 (7.8–19.2)	7.1 (5.6–10.2)	9.7 (5.8–14.8)	7.0 (3.9–10.6)
Later-line anti-EGFR therapy, *n* (%)	13 (25)	11 (26.8)	13 (41.9)	15 (50)
Panitumumab	4 (7.7)	7 (17.1)	8 (25.8)	7 (23.3)
Cetuximab	10 (19.2)	4 (9.8)	5 (16.1)	9 (30)
Other	0 (0)	0 (0)	0 (0)	0 (0)
Later-line anti-VEGF therapy, *n* (%)	19 (36.5)	6 (14.6)	19 (61.3)	10 (33.3)
Bevacizumab	18 (34.6)	5 (12.2)	18 (58.1)	10 (33.3)
Other	1 (1.9)	1 (2.4)	1 (3.2)	0 (0)

5-FU, 5-fluorouracil; bev, bevacizumab; CI, confidence interval; EGFR, epidermal growth factor receptor; IQR, interquartile range; LV, leucovorin; OS, overall survival; PFS, progression-free survival; Pmab, panitumumab; VEGF, vascular endothelial growth factor.

plus 5-FU/LV *vs.* 5-FU/LV alone as maintenance strategies.[26] In the current analysis, panitumumab plus 5-FU/LV maintenance therapy was associated with encouraging median OS and PFS rates, both from randomisation and from the time of oxaliplatin discontinuation.

Although practice-defining data are available regarding bevacizumab-based maintenance therapy, the implications of these remain somewhat unclear. Statistically significant results have been reported with respect to PFS and time-to-failure-of-strategy endpoints. For example, the CAIRO3 and AIO KRK0207 trials suggested that maintenance strategies based on fluoropyrimidine plus bevacizumab might be regarded as standard as they impact on PFS and time-to-failure-of-strategy/PFS-2.[13,14] Similarly, results from a Phase III study of bevacizumab and capecitabine maintenance after discontinuation of oxaliplatin also suggest a potential benefit on PFS.[27] However, OS data from these studies appear conflicting. The AIO KRK0207 trial did not find a difference in OS between treatment groups, although the limited feasibility of sequential therapy prevented the authors from drawing clear conclusions.[14] In CAIRO3, a trend for improved OS failed to reach the level of significance.[13] A Swiss Phase III study of mCRC failed to demonstrate non-inferiority of bevacizumab continuation (after induction with chemotherapy) compared with no continuation, with respect to time-to-progression.[28] Furthermore, the PRODIGE 9 Phase III trial of bevacizumab maintenance treatment found no benefit over observation alone, against a range of endpoints.[29] A meta-analysis of bevacizumab-based maintenance therapy reported improvements in time-to-failure-of-strategy and PFS, and a trend to improvements in OS, compared with complete stop.[30]

As patients in this analysis of maintenance therapy are anti-EGFR-experienced and a selection bias may therefore exist, this should be borne in mind when considering the observed toxicity profiles – patients who discontinued treatment due to unacceptable toxicity were not evaluated. Panitumumab is associated mainly with skin toxicity, and cutaneous side effects of anti-EGFR antibodies can be dose-limiting toxicities. Most clinical trials have focused on folliculitis or acne-like rash, and prophylactic treatment using cyclines, emollients and photoprotection measures are now recommended.[31,32] However, other side effects, such as xerosis or paronychia, may also represent limiting toxicities in patients for whom PFS in first-line treatment exceeds 12 months.[32,33] These toxicities may justify a 'stop-go' strategy for anti-EGFR antibodies, as might the potential emergence of *RAS* mutations or other less common genomic alterations associated with acquired resistance to anti-EGFR therapy.[34,35] Acquired resistance in patients who previously responded to anti-EGFR treatment may occur due to the emergence of *RAS* or *EGFR* ectodomain mutations, suggesting that ongoing monitoring of patients' EGFR status during treatment may be important.[34–36] To this end, it is possible that use of liquid biopsy before commencing maintenance treatment might be valuable in identifying those patients most likely to benefit. The results of the current study support further investigation

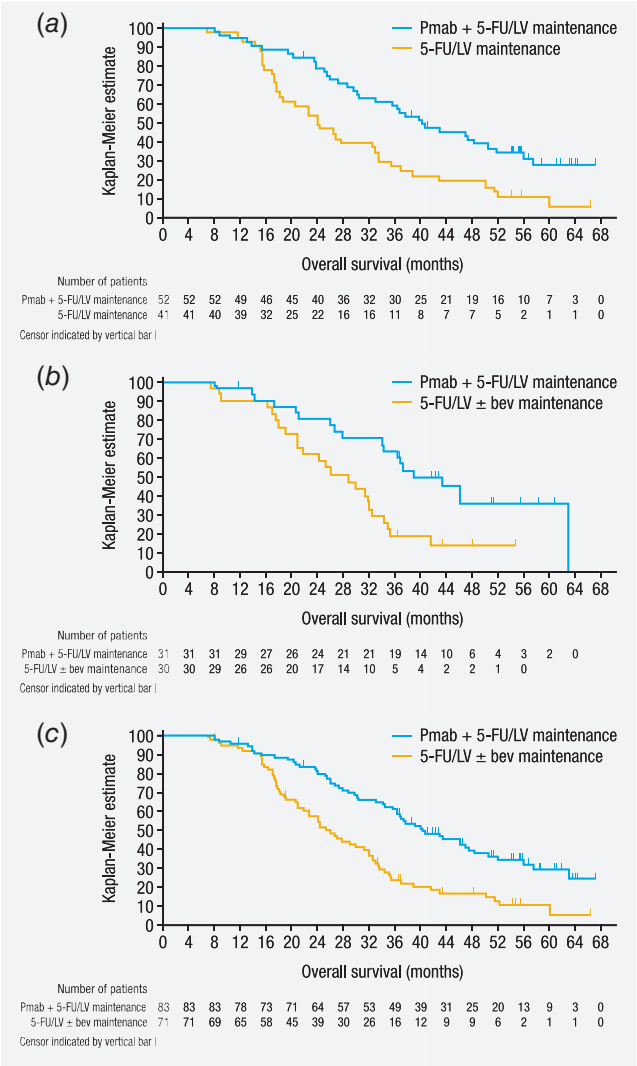

Figure 1. Overall survival from randomisation in (*a*) PRIME, (*b*) PEAK and (*c*) pooled analysis of both trials. **5**-FU, **5**-fluorouracil; bev, bevacizumab; LV, leucovorin; Pmab, panitumumab.

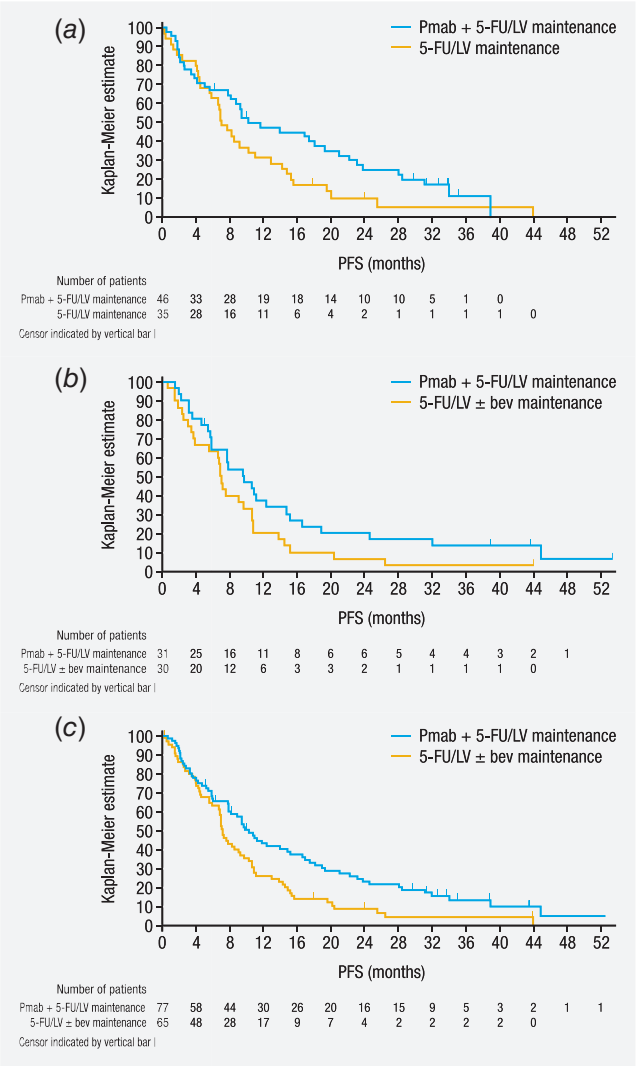

Figure 2. Progression-free survival from oxaliplatin discontinuation (i.e., start of maintenance therapy) in (*a*) PRIME, (*b*) PEAK and (*c*) pooled analysis of both trials. **5**-FU, **5**-fluorouracil; bev, bevacizumab; LV, leucovorin; PFS, progression-free survival; Pmab, panitumumab.

of panitumumab maintenance in *RAS WT* mCRC patients, and prospective Phase II studies are ongoing.[24,26,37]

The authors are aware that this analysis has some limitations, inherent to its retrospective nature. The analyses and results were exploratory and no formal statistical hypothesis or comparisons between groups were made. There were relatively small number of patients in both the panitumumab plus 5-FU/LV maintenance and 5-FU/LV ± bevacizumab maintenance groups and initiation of maintenance therapy occurred later than would be expected in prospective clinical trials. Patients who discontinued oxaliplatin were permitted to reintroduce it during the follow-up period (i.e., 'stop-go' paradigm), which may have affected the outcomes. Patients with early progression did not receive any maintenance treatment and therefore an *a priori* selection of patients with EGFR-dependent/chemosensitive disease existed and is consistent with the high values reached by the survival measures. The finding that patients who received panitumumab plus 5-FU/LV maintenance were more likely to have received ≥9 months of first-line treatment and had generally experienced greater benefit from first-line treatment than those in other groups also suggests the positive selection of patients with panitumumab/chemotherapy-sensitive tumours. Given the limited sample size and the retrospective nature of the study, groups were not perfectly balanced in terms of baseline demographics, for example with respect to *BRAF* mutations, metastases and prior adjuvant therapy.

Our analysis suggests that in a substantial number of patients, no maintenance treatment was administered after

Table 4. Maintenance treatment-emergent adverse events reported in ≥20% of patients in either treatment group in PRIME or PEAK

Maintenance treatment-emergent AEs, *n* (%)	PRIME				PEAK			
	Pmab + 5-FU/LV maintenance (*n* = 52)		5-FU/LV maintenance (*n* = 41)		Pmab + 5-FU/LV maintenance (*n* = 31)		5-FU/LV + bev maintenance (*n* = 30)	
	All AEs	Grade 3+	All AEs	Grade 3+	All AEs	Grade 3+	All AEs	Grade 3+
Any	47 (90.4)	31 (59.6)	36 (87.8)	17 (41.5)	30 (96.8)	15 (48.4)	28 (93.3)	14 (46.7)
Rash	18 (34.6)	6 (11.5)	0 (0.0)	0 (0.0)	15 (48.4)	2 (6.5)	0 (0.0)	0 (0.0)
Diarrhoea	13 (25.0)	1 (1.9)	11 (26.8)	2 (4.9)	16 (51.6)	0 (0.0)	9 (30.0)	0 (0.0)
Fatigue	14 (26.9)	2 (3.8)	5 (12.2)	0 (0.0)	9 (29.0)	1 (3.2)	7 (23.3)	1 (3.3)
Neuropathy, peripheral	10 (19.2)	3 (5.8)	10 (24.4)	5 (12.2)	11 (35.5)	2 (6.5)	4 (13.3)	3 (10.0)
Hypomagnesaemia	10 (19.2)	4 (7.7)	1 (2.4)	0 (0.0)	10 (32.3)	2 (6.5)	1 (3.3)	0 (0.0)
Skin fissures	12 (23.1)	2 (3.8)	0 (0.0)	0 (0.0)	7 (22.6)	0 (0.0)	1 (3.3)	0 (0.0)
Conjunctivitis	11 (21.2)	2 (3.8)	2 (4.9)	0 (0.0)	5 (16.1)	0 (0.0)	1 (3.3)	1 (3.3)
Mucosal inflammation	11 (21.2)	1 (1.9)	2 (4.9)	0 (0.0)	5 (16.1)	0 (0.0)	0 (0.0)	0 (0.0)
Paraesthesia	11 (21.2)	9 (17.3)	9 (22.0)	3 (7.3)	5 (16.1)	2 (6.5)	1 (3.3)	0 (0.0)
Paronychia	11 (21.2)	0 (0.0)	0 (0.0)	0 (0.0)	4 (12.9)	0 (0.0)	0 (0.0)	0 (0.0)
Neutropenia	9 (17.3)	5 (9.6)	5 (12.2)	2 (4.9)	4 (12.9)	1 (3.2)	3 (10.0)	0 (0.0)
Dermatitis acneiform	9 (17.3)	4 (7.7)	0 (0.0)	0 (0.0)	3 (9.7)	0 (0.0)	0 (0.0)	0 (0.0)
Vomiting	8 (15.4)	0 (0.0)	5 (12.2)	0 (0.0)	4 (12.9)	0 (0.0)	3 (10.0)	0 (0.0)
Pruritus	8 (15.4)	1 (1.9)	2 (4.9)	0 (0.0)	1 (3.2)	0 (0.0)	0 (0.0)	0 (0.0)
Anorexia	8 (15.4)	0 (0.0)	3 (7.3)	0 (0.0)	NR	NR	NR	NR
Stomatitis	7 (13.5)	1 (1.9)	2 (4.9)	0 (0.0)	9 (29.0)	0 (0.0)	2 (6.7)	0 (0.0)
Acne	7 (13.5)	2 (3.8)	0 (0.0)	0 (0.0)	7 (22.6)	3 (9.7)	0 (0.0)	0 (0.0)
Asthenia	7 (13.5)	1 (1.9)	3 (7.3)	0 (0.0)	6 (19.4)	0 (0.0)	6 (20.0)	2 (6.7)
Dry skin	6 (11.5)	1 (1.9)	1 (2.4)	0 (0.0)	6 (19.4)	0 (0.0)	0 (0.0)	0 (0.0)
Nausea	7 (13.5)	1 (1.9)	8 (19.5)	0 (0.0)	5 (16.1)	0 (0.0)	5 (16.7)	0 (0.0)
Peripheral sensory neuropathy	7 (13.5)	2 (3.8)	3 (7.3)	1 (2.4)	5 (16.1)	0 (0.0)	3 (10.0)	2 (6.7)
Hypokalaemia	6 (11.5)	3 (5.8)	2 (4.9)	0 (0.0)	5 (16.1)	2 (6.5)	1 (3.3)	0 (0.0)
Decreased appetite	0 (0.0)	0 (0.0)	1 (2.4)	0 (0.0)	8 (25.8)	0 (0.0)	4 (13.3)	0 (0.0)
Nail disorder	6 (11.5)	0 (0.0)	0 (0.0)	0 (0.0)	4 (12.9)	0 (0.0)	0 (0.0)	0 (0.0)
Thrombocytopenia	6 (11.5)	1 (1.9)	3 (7.3)	0 (0.0)	4 (12.9)	0 (0.0)	2 (6.7)	0 (0.0)
Constipation	5 (9.6)	0 (0.0)	2 (4.9)	0 (0.0)	4 (12.9)	0 (0.0)	2 (6.7)	0 (0.0)
Palmar-plantar erythrodysaesthesia syndrome	2 (3.8)	0 (0.0)	3 (7.3)	0 (0.0)	5 (16.1)	0 (0.0)	2 (6.7)	1 (3.3)
Abdominal pain	5 (9.6)	0 (0.0)	4 (9.8)	0 (0.0)	3 (9.7)	0 (0.0)	2 (6.7)	0 (0.0)
Arthralgia	4 (7.7)	0 (0.0)	0 (0.0)	0 (0.0)	3 (9.7)	0 (0.0)	2 (6.7)	0 (0.0)

5-FU, 5-fluorouracil; AE, adverse event; bev, bevacizumab; LV, leucovorin; NR, not recorded; Pmab, panitumumab.

oxaliplatin discontinuation. Various factors may explain these observations, including population bias, but these interesting preliminary findings warrant further investigation of outcomes, including OS, of panitumumab plus 5-FU/LV maintenance therapy in mCRC. Also, patients with best outcomes after intensive treatment were more prevalent in the panitumumab plus 5-FU/LV maintenance groups, opening the way to speculation on how optimal pharmacological cytoreduction might improve the effectiveness of anti-EGFR-based maintenance, or on potential synergistic effects of panitumumab and continued – even if de-escalated – chemotherapy in hyper-responsive selected *RAS* WT patients.

Conclusions

In this retrospective analysis, maintenance of panitumumab plus 5-FU/LV treatment after discontinuation of oxaliplatin was well tolerated and PFS and OS were numerically longer when panitumumab was part of the maintenance regime. Patients in the panitumumab plus 5-FU/LV maintenance groups had a good response to first-line treatment, suggesting that for those patients demonstrating such a response to first-line treatment in clinical practice, maintenance with panitumumab and fluorouracil might be an acceptable treatment paradigm. These results are in concordance with those of previous Phase II trials that investigated anti-EGFR antibodies in maintenance therapy. However, the retrospective design of our study means that it is not possible

to confirm whether the observed clinical benefit is due to the induction treatment (all drugs), the maintenance therapy or both. The analyses also suggest that in a substantial number of patients, no maintenance treatment was administered after oxaliplatin discontinuation. The role of panitumumab maintenance after withdrawal of oxaliplatin should be further investigated in prospective trials that include a biomarker analysis, assessment of OS and assessment of quality of life.

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Authors' contributions

FR contributed to the study design and data collection in PRIME and PEAK. JYD contributed to the study design and data collection in PRIME. RK performed the data analysis. All authors contributed to the interpretation of the data, the preparation and revision of the manuscript and approved the final version.

Availability of data and materials

There is a plan to share data. This may include de-identified individual patient data for variables necessary to address the specific research question in an approved data-sharing request; also related data dictionaries, study protocol, statistical analysis plan, informed consent form and/or clinical study report. Data sharing requests relating to data in this manuscript will be considered after the publication date and (*i*) this product and indication (or other new use) have been granted marketing authorisation in both the United States and Europe, or (*ii*) clinical development discontinues and the data will not be submitted to regulatory authorities. There is no end date for eligibility to submit a data sharing request for these data. Qualified researchers may submit a request containing the research objectives, the Amgen product(s) and Amgen study/studies in scope, endpoints/outcomes of interest, statistical analysis plan, data requirements, publication plan, and qualifications of the researcher(s). In general, Amgen does not grant external requests for individual patient data for the purpose of re-evaluating safety and efficacy issues already addressed in the product labelling. A committee of internal advisors reviews requests. If not approved, a Data Sharing Independent Review Panel will arbitrate and make the final decision. Upon approval, information necessary to address the research question will be provided under the terms of a data sharing agreement. This may include anonymised individual patient data and/or available supporting documents, containing fragments of analysis code where provided in analysis specifications. Further details are available at the following: http://www.amgen.com/datasharing.

References

1. European Medicines Agency. Summary of product characteristics. Vectibix 20 mg/mL concentrate for solution for infusion. 2016 [cited 2018 Nov 8]; Available from: https://www.medicines.org.uk/emc/medicine/20528
2. Van Cutsem E, Cervantes A, Adam R, et al. ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. *Ann Oncol* 2016;27:1386–422.
3. Douillard JY, Oliner KS, Siena S, et al. Panitumumab-FOLFOX4 treatment and *RAS* mutations in colorectal cancer. *N Engl J Med* 2013;369:1023–34.
4. Rivera F, Karthaus M, Hecht JR, et al. Final analysis of the randomised PEAK trial: overall survival and tumour responses during first-line treatment with mFOLFOX6 plus either panitumumab or bevacizumab in patients with metastatic colorectal carcinoma. *Int J Colorectal Dis* 2017;32:1179–90.
5. Schwartzberg LS, Rivera F, Karthaus M, et al. PEAK: a randomized, multicenter phase II study of panitumumab plus modified fluorouracil, leucovorin, and oxaliplatin (mFOLFOX6) or bevacizumab plus mFOLFOX6 in patients with previously untreated, unresectable, wild-type *KRAS* exon 2 metastatic colorectal cancer. *J Clin Oncol* 2014;32:2240–7.
6. Douillard JY, Siena S, Cassidy J, et al. Randomized, phase III trial of panitumumab with infusional fluorouracil, leucovorin, and oxaliplatin (FOLFOX4) versus FOLFOX4 alone as first-line treatment in patients with previously untreated metastatic colorectal cancer: the PRIME study. *J Clin Oncol* 2010;28:4697–705.
7. Saltz LB, Clarke S, Diaz-Rubio E, et al. Bevacizumab in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer: a randomized phase III study. *J Clin Oncol* 2008;26:2013–9.
8. Modest DP, Stintzing S, von Weikersthal LF, et al. Impact of subsequent therapies on outcome of the FIRE-3/AIO KRK0306 trial: first-line therapy with FOLFIRI plus cetuximab or bevacizumab in patients with *KRAS* wild-type tumors in metastatic colorectal cancer. *J Clin Oncol* 2015;33:3718–26.
9. Tournigand C, Cervantes A, Figer A, et al. OPTIMOX1: a randomized study of FOLFOX4 or FOLFOX7 with oxaliplatin in a stop-and-go fashion in advanced colorectal cancer – a GERCOR study. *J Clin Oncol* 2006;24:394–400.
10. Chibaudel B, Maindrault-Goebel F, Lledo G, et al. Can chemotherapy be discontinued in unresectable metastatic colorectal cancer? The GERCOR OPTIMOX2 study. *J Clin Oncol* 2009;27:5727–33.
11. Kasi PM, Grothey A. Chemotherapy maintenance. *Cancer J* 2016;22:199–204.
12. Grothey A, Hart LL, Rowland KM, et al. Intermittent oxaliplatin (oxali) administration and time-to-treatment-failure (TTF) in metastatic colorectal cancer (mCRC): final results of the phase III CONcePT trial. *J Clin Oncol* 2008;26:4010.
13. Simkens LH, van Tinteren H, May A, et al. Maintenance treatment with capecitabine and bevacizumab in metastatic colorectal cancer (CAIRO3): a phase 3 randomised controlled trial of the Dutch colorectal cancer group. *Lancet* 2015;385:1843–52.
14. Hegewisch-Becker S, Graeven U, Lerchenmuller CA, et al. Maintenance strategies after first-line oxaliplatin plus fluoropyrimidine plus bevacizumab for patients with metastatic colorectal cancer (AIO 0207): a randomised, non-inferiority, open-label, phase 3 trial. *Lancet Oncol* 2015;16:1355–69.
15. Alfonso PG, Benavides M, Ruiz AS, et al. Phase II study of first-line mfolfox plus cetuximab (C) for 8 cycles followed by mFOLFOX plus C or single agent (s/a) c as maintenance therapy in patients (p) with metastatic colorectal cancer (MCRC): the MACRO-2 trial (Spanish cooperative group for the treatment of digestive tumors [TTD]). *Ann Oncol* 2014;25:iv168.
16. Wasan H, Meade AM, Adams R, et al. Intermittent chemotherapy plus either intermittent or continuous cetuximab for first-line treatment of patients with *KRAS* wild-type advanced colorectal cancer (COIN-B): a randomised phase 2 trial. *Lancet Oncol* 2014;15:631–9.
17. Pfeiffer P, Sorbye H, Qvortrup C, et al. Maintenance therapy with cetuximab every second week in the first-line treatment of metastatic colorectal cancer: the NORDIC-7.5 study by the Nordic colorectal cancer biomodulation group. *Clin Colorectal Cancer* 2015;14:170–6.
18. Rivera F, Bachet J, Modest D, et al. Outcomes in patients receiving maintenance therapy in two

panitumumab (Pmab) first-line trials for metastatic colorectal cancer (mCRC). *Ann Oncol* 2017; 28:519P.
19. Allegra C, Blanke C, Buyse M, et al. End points in advanced colon cancer clinical trials: a review and proposal. *J Clin Oncol* 2007;25:3572–5.
20. Hubbard JM, Grothey A. When less is more: maintenance therapy in colorectal cancer. *Lancet* 2015;385:1808–10.
21. Chibaudel B, Bonnetain F, Shi Q, et al. Alternative end points to evaluate a therapeutic strategy in advanced colorectal cancer: evaluation of progression-free survival, duration of disease control, and time to failure of strategy – an aide et Recherche en Cancerologie digestive group study. *J Clin Oncol* 2011;29:4199–204.
22. ClinicalTrials.gov. Safety and efficacy study of mFOLFOX6 + panitumumab combination therapy and 5-FU/LV + panitumumab combination therapy in patients with Chemotherapy-naïve unresectable advanced recurrent colorectal carcinoma (SAPPHIRE). 2017 [cited 2018 Nov 8]; Available from: https://clinicaltrials.gov/show/NCT02337946
23. Nakamura M, Munemoto Y, Takahashi M, et al. SAPPHIRE: a randomized phase II study of mFOLFOX6 + panitumumab versus 5-FU/LV + panitumumab after 6 cycles of frontline mFOLFOX6 + panitumumab in patients with colorectal cancer. *J Clin Oncol* 2018;36:729.
24. ClinicalTrials.gov. Panitumumab-based maintenance in patients with *RAS* wild-type, metastatic colorectal cancer (VALENTINO). 2016 [cited 2018 Nov 8]; Available from: https://clinicaltrials.gov/ct2/show/NCT02476045
25. Pietrantonio F, Caporale C, Berenato R, et al. First-line FOLFOX plus panitumumab followed by 5-FU/LV plus panitumumab or single-agent panitumumab as maintenance therapy in patients with *RAS* wild-type metastatic colorectal cancer (mCRC): the VALENTINO study. *J Clin Oncol* 2018;36: abstr 3505.
26. ClinicalTrials.gov. Maintenance therapy with 5-FU/FA plus panitumumab vs. 5-FU/FA alone after prior induction and re-induction after progress for 1st-line treatment of metastatic colorectal cancer (PanaMa). 2017 [cited 2018 Nov 8]; Available from: https://clinicaltrials.gov/ct2/show/NCT01991873
27. Yalcin S, Uslu R, Dane F, et al. Bevacizumab + capecitabine as maintenance therapy after initial bevacizumab + XELOX treatment in previously untreated patients with metastatic colorectal cancer: phase III 'Stop and Go' study results – a Turkish oncology group trial. *Oncology* 2013;85:328–35.
28. Koeberle D, Betticher DC, von Moos R, et al. Bevacizumab continuation versus no continuation after first-line chemotherapy plus bevacizumab in patients with metastatic colorectal cancer: a randomized phase III non-inferiority trial (SAKK 41/06). *Ann Oncol* 2015;26:709–14.
29. Aparicio T, Ghiringhelli F, Boige V, et al. Bevacizumab maintenance versus no maintenance during chemotherapy-free intervals in metastatic colorectal cancer: a randomized phase III trial (PRODIGE 9). *J Clin Oncol* 2018;36:674–81.
30. Tamburini E, Rudnas B, Santelmo C, et al. Maintenance based bevacizumab versus complete stop or continuous therapy after induction therapy in first line treatment of stage IV colorectal cancer: a meta-analysis of randomized clinical trials. *Crit Rev Oncol Hematol* 2016;104:115–23.
31. Bachet JB, Peuvrel L, Bachmeyer C, et al. Folliculitis induced by EGFR inhibitors, preventive and curative efficacy of tetracyclines in the management and incidence rates according to the type of EGFR inhibitor administered: a systematic literature review. *Oncologist* 2012;17:555–68.
32. Lacouture ME, Anadkat MJ, Bensadoun RJ, et al. Clinical practice guidelines for the prevention and treatment of EGFR inhibitor-associated dermatologic toxicities. *Support Care Cancer* 2011;19: 1079–95.
33. Peuvrel L, Bachmeyer C, Reguiai Z, et al. Semiology of skin toxicity associated with epidermal growth factor receptor (EGFR) inhibitors. *Support Care Cancer* 2012;20:909–21.
34. Misale S, Yaeger R, Hobor S, et al. Emergence of *KRAS* mutations and acquired resistance to anti-EGFR therapy in colorectal cancer. *Nature* 2012; 486:532–6.
35. Spindler KL, Pallisgaard N, Andersen RF, et al. Changes in mutational status during third-line treatment for metastatic colorectal cancer – results of consecutive measurement of cell free DNA, KRAS and BRAF in the plasma. *Int J Cancer* 2014;135:2215–22.
36. Arena S, Bellosillo B, Siravegna G, et al. Emergence of multiple *EGFR* extracellular mutations during cetuximab treatment in colorectal cancer. *Clin Cancer Res* 2015;21:2157–66.
37. Fédération Francophone de Cancérologie Digestive. Signature de la nouvelle charte prodige. 2017 [cited 2018 Nov 8]; Available from: http://www.ffcd.fr/DOC/LETTRE/Lettre_Fevrier2017.pdf