Curr Colorectal Cancer Rep (2017) 13:257–263
DOI 10.1007/s11888-017-0372-7

Anti-EGFR and Anti-VEGF Agents in First-Line Therapy for Advanced Colorectal Cancer

Aaron P. Mitchell[1] · **Hanna K. Sanoff**[1]

Published online: 21 April 2017

Abstract Outcomes for metastatic colorectal cancer have improved progressively with the incorporation of new drugs into standard treatment regimens. Most recently, targeted therapies against VEGF and EGFR have improved upon the prior standard for first-line therapy with FOLFOX or FOLFIRI. As attempts to combine anti-VEGF and anti-EGFR drugs have been unsuccessful, it is necessary to choose between them when beginning first-line therapy. This review summarizes the existing literature to best inform this decision. To date, three head-to-head trials have compared anti-EGFR and anti-VEGF therapy in RAS wild-type patients: PEAK, FIRE-3, and CALGB/SWOG 80405. PEAK and FIRE-3 suggested a survival advantage for anti-EGFR therapy over anti-VEGF therapy, though CALGB/SWOG 80405 did not. Results have emerged recently to suggest that tumors arising from the right colon are resistant to anti-EGFR therapy, and that any advantage of anti-EGFR therapy over anti-VEGF therapy may be limited to left-sided tumors.

Keywords Colorectal cancer · Targeted therapy · Anti-VEGF · Anti-EGFR · Panitumumab · Cetuximab · Bevacizumab

Topical Collection on *Systemic Therapies in Colorectal Cancer*

✉ Hanna K. Sanoff
hanna_sanoff@med.unc.edu

Aaron P. Mitchell
aaron.mitchell@unchealth.unc.edu

[1] Division of Hematology/Oncology, Department of Medicine, University of North Carolina, 3rd Floor, Physicians Office Building, 170 Manning Drive, Chapel Hill, NC 27599, USA

Introduction

Colorectal cancer is the second leading cause of cancer-related mortality in the USA, responsible for over 49,000 deaths annually [1]. Approximately 20% of cases are metastatic at the time of initial diagnosis [2], and it is these cases that cause the majority of colorectal cancer deaths. The prognosis of metastatic colorectal cancer (mCRC) has significantly improved in recent decades due to advances in medical therapy. Historical survival times of mere months improved to over 1 year as 5-FU-based therapy became the standard of care, and improved further to nearly 2 years with the adoption of 5-FU-based doublet therapies including oxaliplatin or irinotecan [3]. The recent development of targeted therapies promises to continue to improve mCRC outcomes.

Bevacizumab, a monoclonal antibody against vascular endothelial growth factor (VEGF), became the first targeted agent approved for first-line therapy of mCRC in 2004. Bevacizumab was studied in a randomized, double-blinded trial conducted in patients with good performance status (ECOG 0–1) and was powered to detect a difference in overall survival [4]. The addition of bevacizumab to irinotecan, bolus 5-FU, and leucovorin (IFL) chemotherapy was found to increase median overall survival (OS) from 15.6 to 20.3 months, and the inclusion of bevacizumab in first-line therapy became the standard of care for patients without contraindications. Bevacizumab has also shown efficacy in combination with oxaliplatin-containing first-line regimens, increasing progression-free survival (PFS) from 19.9 to 21.3 months vs. placebo when added to FOLFOX or capecitabine plus oxaliplatin [5].

Cetuximab, a monoclonal antibody against the epidermal growth factor receptor (EGFR), was initially approved for refractory disease and then later approved for first-line therapy in 2012 based on the results of the randomized, open-label

CRYSTAL trial, which was powered for PFS [6]. Mature analysis of the CRYSTAL trial eventually showed that the addition of cetuximab to FOLFIRI increased median OS to 19.9 from 18.6 months [7]. However, retrospective analysis based on tumor mutation status found no benefit in the 35.6% of patients with KRAS-mutant tumors and a more pronounced benefit (23.5 vs. 20.0 months median OS) in patients with KRAS wild-type tumors, supporting an FDA recommendation that cetuximab not be used in the treatment of KRAS-mutant tumors.

Finally, panitumumab, also an EGFR-directed monoclonal antibody, received approval for first-line treatment of mCRC in 2014 based on the results of the PRIME trial. This was an open-label, randomized trial that studied panitumumab added to FOLFOX in patients who had not previously received oxaliplatin during adjuvant therapy [8]. Initially powered to detect a PFS difference in all patients, the PRIME protocol was later amended to analyze for a PFS difference on the basis of KRAS mutation status. Similar to the CRYSTAL trial, mature analysis showed a median OS benefit (23.8 vs. 19.4 months) in the 60% of patients with KRAS wild-type tumors [9].

With the efficacy of these three agents demonstrated individually, efforts have been made to combine anti-VEGF and anti-EGFR in first-line therapy to potentially improve mCRC outcomes further. However, this strategy has not been successful in clinical trials. Two separate phase III trials evaluated the addition of anti-EGFR therapy to 5-FU-based chemotherapy plus bevacizumab in the first-line setting, and found that adding either cetuximab [10] or panitumumab [11] brought no improvement in survival while increasing toxicity. This detrimental effect has been consistent across smaller studies [12] and meta-analysis [13].

Given the firm experimental evidence supporting the addition of either, but not both, anti-VEGF or anti-EGFR agents to first-line chemotherapy, the next obvious question is which of these drug classes should be preferred? Several randomized trials have been conducted to address this question directly (Table 1).

Clinical Trial Results

The PEAK Trial

The first completed clinical trial to compare anti-VEGF to anti-EGFR therapy head-to-head in the first-line setting was the PEAK trial [14••], which began enrolling patients in 2009. This open-label, phase II trial compared panitumumab versus bevacizumab, in combination with FOLFOX, for treatment-naïve mCRC. As the KRAS-dependent efficacy of anti-EGFR agents was well understood by this time, only KRAS wild-type patients were enrolled. Specifically, patients needed to be

Table 1 Characteristics of the three head-to-head trials of anti-EGFR and anti-VEGF therapy

Study	Year begun	Study size	Population	Study arms	Response rate (%)	Median PFS (months)	Median OS (months)	HR for death
PEAK [14••]	2009	285	KRAS exon 2 (codons 12, 13) WT	Panitumumab + FOLFOX	58	10.9 (95% CI 9.4–13.0)	34.2 (95% CI 26.6—not reached)	0.62 (95% CI 0.44–0.89) (panitumumab vs. bevacizumab)
				Bevacizumab + FOLFOX	54	10.1 (95% CI 9.0–12.6)	24.3 (95% CI 21.0–29.2)	
FIRE-3 [15••]	2007	592	KRAS exon 2 (codons 12, 13) WT	Cetuximab + FOLFIRI	62	10.0 (95% CI 8.8–10.8)	28.7 (95% CI 24.0–36.6)	0.77 (95% CI 0.62–0.96) (cetuximab vs. bevacizumab)
				Bevacizumab + FOLFIRI	58	10.3 (95% CI 9.8–11.3)	25.0 (95% 22.7–27.6)	
CALGB/SWOG 80405 [18••]	2005	1137	KRAS exon 2 (codons 12, 13) WT	Cetuximab + FOLFOX or FOLFIRI	NR	10.45 (9.66–11.33)	29.9 (95% CI 27.6–31.2)	0.92 (95% CI 0.78–1.09) (bevacizumab vs. cetuximab)
				Bevacizumab + FOLFOX or FOLFIRI	NR	10.84 (9.86–11.4)	29.0 (95% CI 25.7–31.2)	

For each study, results are reported for the primary pre-specified analysis of KRAS exon 2 wild-type patients, rather than any secondary analyses of all-RAS wild-type groups

wild type at KRAS exon 2 at enrollment, while additional testing and subgroup analysis for mutations at other KRAS and NRAS exons was done post-hoc. Two hundred eighty-five patients were enrolled and randomized.

The PEAK trial found that panitumumab was superior to bevacizumab by median OS (34.2 vs. 24.3 months, HR 0.62, 95% CI 0.44, 0.89). Interestingly, there was not significant improvement in PFS (10.9 vs. 10.1 months, respectively, HR 0.87, 95% CI 0.65–1.17), which was the primary endpoint of the study. In the subgroup of patients who were wild type at all RAS exons, the magnitude of the OS benefit was increased (41.3 vs. 28.9 months, HR 0.63, 95% CI 0.39, 1.02), and panitumumab improved median PFS (13.0 vs. 9.5 months) in these patients as well.

The FIRE-3/AIO KRK0306 Trial

The open-label, phase III FIRE-3 trial compared cetuximab versus bevacizumab, in combination with FOLFIRI, for mCRC in patients who had not received prior treatment other than adjuvant chemotherapy [15••]. This trial began enrolling in 2007 without regard to KRAS mutation status, though in response to evidence regarding the KRAS-dependent efficacy of anti-EGFR therapy, enrollment was later restricted to patients with KRAS exon 2 wild-type tumors, and analysis was stratified with respect to KRAS status. The final analytic cohort of KRAS exon 2 wild-type mCRC contained 592 patients, giving approximately 80% power to detect an improvement in the primary endpoint of objective response from 50% with FOLFIRI-bevacizumab to 62% with FOLFIRI-cetuximab.

The FIRE-3 trial failed to meet its primary endpoint, with response rate of 62% in the cetuximab group and 58% of the bevacizumab group (OR 1.18, 95% CI 0.85, 1.64, $p = 0.18$). Similar to the results of the PEAK trial, there was no significant difference between anti-EGFR therapy (cetuximab) and bevacizumab with respect to PFS (10.0 months for cetuximab vs. 10.3 months for bevacizumab, HR 1.06, 95% CI 0.88, 1.26). However, also like the PEAK trial, anti-EGFR therapy was superior in the secondary outcome of OS (28.7 vs. 25.0 months, HR 0.77, 95% CI 0.62, 0.96) despite the lack of difference in PFS.

In order to better understand why cetuximab-treated patients had significantly better survival despite similar response rate and PFS as bevacizumab-treated patients, the FIRE-3 investigators evaluated the effect of tumor dynamics and post-progression therapy on survival. In an exploratory analysis with centralized radiology review of the subgroup of patients with cancers wild-type at all RAS loci, early tumor response (≥20% reduction by first scan) was more common in cetuximab-treated than bevacizumab-treated patients (68 vs. 49%, OR 2.22, 95% CI 1.41, 3.47) and the depth of response was greater (−49 vs. −32%, $p < 0.0001$) despite similar time to and duration of response [16]. In this secondary analysis of all RAS wild-type cancers, survival benefit from cetuximab was more pronounced (33.1 vs. 25.0 months, HR 0.70, 95% CI 0.54, 0.90) [16].

Although similar proportions of FIRE-3 patients who received first-line cetuximab later received bevacizumab in second-line therapy (47%) as vice-versa (52%), patients who had received cetuximab initially had better outcomes overall [17]. Regardless of the response/duration of first-line therapy, patients who had received first-line cetuximab had improved PFS (6.5 vs. 3.2 months) and OS (16.3 vs. 13.2 months) from the time of initiation of *second-line* therapy. The trial authors hypothesized a biological mechanism for these differences, by which initial anti-EGFR therapy might "prime" tumors to respond better to later treatments.

CALGB/SWOG 80405

The third and largest prospective trial to compare anti-VEGF and anti-EGFR therapy in the first-line setting, CALGB/SWOG 80405, randomized patients to cetuximab or bevacizumab, with either FOLFOX or FOLFIRI per physician preference. CALGB/SWOG 80405 also initially contained a third arm in which patients received both cetuximab and bevacizumab; this arm was dropped in response to results demonstrating that combining these agents was harmful, as discussed above. As with FIRE-3, it also narrowed enrollment to patients with KRAS wild-type tumors (at exon 2 codons 12 and 13) in response to evidence that cetuximab was efficacious in this group only. The final analytic cohort of KRAS wild-type tumors contained 1137 patients [18••].

As with PEAK and FIRE-3, CALGB/SWOG 80405 failed to meet its primary endpoint, which in this case was overall survival. Outcomes between cetuximab-treated and bevacizumab-treated patients were not significantly different with respect to OS (29.9 vs. 29.0 months, respectively, HR 0.92, 95% CI 0.78, 1.09) or PFS (10.5 vs. 10.8 months). In subsequent reports restricting to an all-RAS wild-type population (e.g., excluding an additional 15% of patients with mutations in KRAS exons 3, 4 or NRAS exons 2, 3, 4), overall survival and progression-free survival remained the same between cetuximab- and bevacizumab-treated patients, though overall response rate favored cetuximab (68.6% versus 53.6%, $p < 0.01$) [19].

Meta-Analysis

Though other comparisons have been made among the anti-VEGF and anti-EGFR agents in observational or second-line therapy settings, these three trials—PEAK, FIRE-3, and CALGB/SWOG 80405—comprise all existing prospective, randomized data comparing these drugs in first-line therapy

for mCRC. Due to the different conclusions reached by these studies, with PEAK and FIRE-3 supporting anti-EGFR therapy over anti-VEGF therapy for KRAS wild-type patients but CALGB/SWOG 80405 showing no difference, several attempts have been made to meta-analyze their results to try to reach a consensus on the preferred first-line strategy.

Meta-analyses of these three trials have tended to reach similar results [20–23]. In line with the results of the individual trials, these analyses have not found a difference between anti-EGFR and anti-VEGF therapy with respect to PFS. Additionally, the overall reduction in death among all-RAS wild-type patients was similar across the meta-analyses, with reported hazard ratios of anti-EGFR vs. anti-VEGF therapy of 0.77 (95% CI 0.63, 0.95) [20], 0.80 (95% CI 0.68, 0.93) [21], 0.78 (95% CI 0.66, 0.93) [22], and 0.80 (95% CI 0.69, 0.92) [23].

Another study used a network meta-analysis technique to compare anti-EGFR and anti-VEGF therapy by analyzing not only those trials that compared the therapies head-to-head, but also those that compared anti-EGFR + chemotherapy or anti-VEGF + chemotherapy to chemotherapy alone [24•]. The authors first conducted a pairwise direct meta-analysis, including only the same three randomized trials that compared the drugs head-to-head. This analysis was consistent with the results of other meta-analyses, finding no difference in PFS (HR for progression 1.02, 95% CI 0.93–1.13) but superiority of anti-EGFR therapy in OS (HR for death, 0.79, 95% CI 0.65–0.98). However, when trials comparing either drug class with chemotherapy to chemotherapy alone were incorporated in the combined network meta-analysis, these results changed significantly. Comparing anti-EGFR to anti-VEGF therapy, PFS appeared to favor anti-VEGF therapy (HR for progression 1.11, 95% CR 0.92–1.36) and OS appeared to favor anti-EGFR therapy (HR for death 0.91, 95% CR 0.75–1.09), though neither difference was statistically significant.

Impact of Tumor Location on Anti-EGFR Therapy

During the course of the PEAK, FIRE-3, and CALGB/SWOG 80405 trials, the importance of RAS mutation status on the efficacy of anti-EGFR therapy became apparent. This information has allowed for a more selective use of these drugs within a narrower group of patients who are most likely to benefit, while avoiding additional toxicity in those unlikely to do so. However, subsequent analysis has elucidated an additional disease factor that appears to be valuable in predicting benefit from anti-EGFR therapy: the location of the primary tumor within the colon (Table 2).

The difference between right-sided and left-sided tumors in terms of patient prognosis was highlighted at the 2016 American Society of Clinical Oncology annual meeting and in follow-up publications. An analysis of the SEER tumor registry found a significantly greater risk of death for tumors arising from the right colon compared to the left colon or rectum [25]. Comparing right-sided to left-sided tumors, the hazard ratio for death was 1.20 (95% CI 1.15, 1.25) for stage IV and 1.17 (95% CI 1.11, 1.23) for stage III; this difference persisted after adjustment for other patient-level factors.

Investigating possible mechanisms to explain this difference, further research was presented at the same meeting investigating the importance of tumor location on response to systemic therapy. Analyzing data from CALGB/SWOG 80405 retrospectively, in addition to offering prognostic information, primary tumor location within the colon appeared to offer predictive information about the effectiveness of cetuximab and bevacizumab [26•]. With the caveat that these were not pre-specified subgroups, patients with left-sided tumors had considerably better survival overall, and in these patients cetuximab was superior to bevacizumab, with median OS of 37.5 vs. 32.1 months, respectively (HR 0.82, 95% CI 0.69, 0.96). However, in right-sided tumors, cetuximab appeared inferior to bevacizumab, with median OS of 16.4 vs. 24.5 (HR 1.26, 95% CI 0.98, 1.63). Differences in PFS were smaller but trended in the same direction.

A similar retrospective analysis of the CRYSTAL and FIRE-3 trials has since been published [27•]. Among the RAS wild-type patients within CRYSTAL, the benefit of adding cetuximab to FOLFIRI appeared to be limited to patients with left-sided tumors. Patients with left-sided tumors had median OS of 28.7 months with FOLFIRI + cetuximab, compared to 21.7 months with FOLFIRI alone (HR 0.65, 95% CI 0.50, 0.86). However, the magnitude of the benefit was much reduced in right-sided tumors, with median OS of 18.5 months for FOLFIRI + cetuximab and 15.0 months for FOLFIRI alone (HR 1.08, 95% CI 0.65, 1.81). Analysis of FIRE-3 with respect to tumor site yielded similar results as that of CALGB/SWOG 80405. Treatment with FOLFIRI + cetuximab was superior to FOLFIRI + bevacizumab for left-sided tumors, with median OS of 38.3 vs. 28.0 months (HR 0.63, 95% CI 0.48, 0.85). In right-sided tumors, the direction of benefit was reversed, with bevacizumab appearing superior in this population; median OS was 18.3 months for FOLFIRI + cetuximab and 23.0 months for FOLFIRI + bevacizumab (HR 1.44, 95% CI 0.81, 2.11). This has also been confirmed in a meta-analysis of 13 first-line, randomized trials that collected data on primary tumor location [28••]. While not yet prospectively validated, the consistent findings across multiple trials and observational registries lend strong support to the notion that primary tumor location is an independent prognostic factor in mCRC, and that the effect of EGFR inhibition differs by primary site. The poorer prognosis of right-sided tumors, as well as their resistance to anti-EGFR therapy, is likely due to underlying pathobiological differences. Right-sided tumors are more likely to carry BRAF mutations [29], a poor overall prognostic marker, and are also

Table 2 Impact of primary tumor location on efficacy of anti-EGFR and anti-VEGF therapies

Study	Source data	Targeted drugs compared	Median OS, right-sided tumors (months)	Median OS, left-sided tumors (months)	HR for death
Venook et al. [26•]	CALGB/SWOG 80405	Cetuximab + FOLFOX or FOLFIRI	16.4	37.5	1.97 (95% CI 1.56, 2.48)
		Bevacizumab + FOLFOX or FOLFIRI	24.5	32.1	1.26 (95% CI 1.00, 1.58)
Tejpar et al. [27•]	FIRE-3 (CRYSTAL trial not shown)	Cetuximab + FOLFIRI	18.3	38.3	2.84 (95% CI 1.86, 4.33)
		Bevacizumab + FOLFIRI	23.0	28.0	1.48 (95% CI 1.02, 2.16)
			HR for death, EGFR vs. VEGF, right-sided tumors	HR for death, EGFR vs. VEGF, left-sided tumors	
Holch et al. [28••]	CALGB/SWOG 80405, FIRE-3, PEAK	Anti-EGFR + FOLFOX or FOLFIRI, vs. anti-VEGF + FOLFOX or FOLFIRI	1.3 (95% CI 0.93, 1.74)	0.71 (95% CI 0.58, 0.85)	

Overall survival times are shown for KRAS wild-type populations only. Tumors arising from the transverse colon were excluded from one study [26•] and classified as right-sided in another [27•]

more likely to have downregulation of EREG and AREG by hypermethylation, the gene products of which are important mediators of response to anti-EGFR therapy [30]. Tumors arising from the transverse colon have generally been classified as right-sided, though this classification is not uniform, and whether these tumors tend to behave more like left-sided or right-sided tumors is not clear from studies done thus far and is an area for future research.

Literature Summary

Results from the three completed clinical trials allow us to reach several conclusions regarding the use of anti-EGFR and anti-VEGF agents in the treatment of mCRC, while several important questions remain regarding the biological mechanisms that result in the different activity profiles of these two drug classes.

The CRYSTAL trial first observed lack of benefit from adding cetuximab to chemotherapy in patients with specific KRAS mutations; the results of PRIME, FIRE-3, and CALGB/SWOG 80405 have demonstrated the same to be true with all RAS mutations. Therefore, from the completed trials in first-line therapy of mCRC, we can conclude that extended RAS testing is essential before instituting anti-EGFR therapy, and anti-EGFR therapy should not be used in patients with any RAS mutation. The results of RAS testing also add important prognostic information.

The three trials, PEAK, FIRE-3, and CALGB/SWOG 80405, that compared cetuximab/panitumuamb to bevacizumab in combination with chemotherapy in the first-line setting all failed to meet their primary endpoint. PEAK and FIRE-3 reported similar response rates and progression-free survival between these two regimens. Although anti-EGFR therapy improved survival in PEAK and FIRE3, the largest of the head-to-head trials, CALGB/SWOG 80405, failed to detect an advantage of anti-EGFR therapy over anti-VEGF therapy. Therefore, the superiority of anti-EGFR therapy in RAS wild-type mCRC was not firmly established from the primary analyses of these trials; either anti-EGFR or anti-VEGF therapy would be appropriate in RAS wild-type patients.

One proposed explanation to reconcile the apparent OS benefit and lack of PFS benefit of anti-EGFR compared to anti-VEGF therapy is that targeting EGFR primes tumors to respond better to later lines of therapy. The effect of anti-EGFR therapy itself may be comparable to anti-VEGF (explaining the equivalent PFS), while the effect of later lines of therapy may be increased (explaining the improved OS among patients treated with anti-EGFR agents first). There is some empirical evidence for this hypothesis from retrospective analysis of FIRE-3 results [17]. The observation in animal models that anti-EGFR targeting results in upregulation of VEGF [31] provides a mechanism for how first-line treatment with anti-EGFR therapy might make second-line therapy with bevacizumab more effective, and has been proposed as an explanation of the FIRE-3 results. More study will be needed to support this hypothesis, as well as how best to capitalize on the "priming" effect of anti-EGFR therapy in clinical practice in terms of dosing schedules and duration of treatment.

Given the inconsistent overall survival data from these head-to-head trials, the observed differential effect of EGFR inhibition across different primary tumor sites should be considered when selecting first-line therapy. For right-sided

tumors, retrospective analyses of the CRYSTAL, FIRE-3 [27•], and CALGB/SWOG 80405 [26•] trials all suggest that the added benefit of anti-EGFR therapy to standard chemotherapy is minimal, and inferior to that of bevacizumab. For left-sided tumors, cetuximab appears superior, resulting in longer survival than bevacizumab in both phase III trials.

In addition, the PARADIGM study of FOLFOX + panitumumab vs. FOLFOX + bevacizumab in first-line treatment of RAS wild-type mCRC began enrolling patients in 2015 and is ongoing. PARADIGM will hopefully shed additional light onto the question of tumor sidedness question, and whether the superiority of anti-EGFR therapy in RAS wild-type, left-sided tumors continues to be demonstrated.

Conclusions

- Patients with treatment-naïve mCRC who are candidates for chemotherapy and have RAS-mutated tumors should receive FOLFOX- or FOLFIRI-based chemotherapy combined with bevacizumab in the absence of contraindications.
- Patients with treatment-naïve mCRC who are candidates for chemotherapy and have RAS wild-type tumors arising from the right colon should receive FOLFOX or FOLFIRI combined with bevacizumab.
- Patients with treatment-naïve mCRC who are candidates for chemotherapy and have RAS wild-type tumors arising from the left colon should receive FOLFOX or FOLFIRI combined with anti-EGFR therapy, although bevacizumab is a reasonable alternative if anti-EGFR therapy is not tolerated.

Compliance with Ethical Standards

Conflict of Interest Aaron P. Mitchell declares that he has no conflict of interest. Hanna K. Sanoff has received research support through grants from Bayer, Novartis, Merck, Precision Biologics, and Immunomedics.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
• Of importance
•• Of major importance

1. Cancer stat facts: colon and rectum cancer. (Surveillance, Epidemiology, and End Results Program (SEER)).
2. Cook AD, Single R, McCahill LE. Surgical resection of primary tumors in patients who present with stage IV colorectal cancer: an analysis of surveillance, epidemiology, and end results data, 1988 to 2000. Ann Surg Oncol. 2005;12:637–45.
3. Gustavsson B, et al. A review of the evolution of systemic chemotherapy in the management of colorectal cancer. Clin Colorectal Cancer. 2015;14:1–10.
4. Hurwitz H, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med. 2004;350:2335–42.
5. Saltz LB, 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 Off J Am Soc Clin Oncol. 2008;26:2013–9.
6. Van Cutsem E, et al. Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. N Engl J Med. 2009;360:1408–17.
7. Van Cutsem E, et al. Cetuximab plus irinotecan, fluorouracil, and leucovorin as first-line treatment for metastatic colorectal cancer: updated analysis of overall survival according to tumor KRAS and BRAF mutation status. J Clin Oncol Off J Am Soc Clin Oncol. 2011;29:2011–9.
8. Douillard J-Y, 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 Off J Am Soc Clin Oncol. 2010;28:4697–705.
9. Douillard JY, et al. Final results from PRIME: randomized phase III study of panitumumab with FOLFOX4 for first-line treatment of metastatic colorectal cancer. Ann Oncol Off J Eur Soc Med Oncol. 2014;25:1346–55.
10. Tol J, et al. Chemotherapy, bevacizumab, and cetuximab in metastatic colorectal cancer. N Engl J Med. 2009;360:563–72.
11. Hecht JR, et al. A randomized phase IIIB trial of chemotherapy, bevacizumab, and panitumumab compared with chemotherapy and bevacizumab alone for metastatic colorectal cancer. J Clin Oncol Off J Am Soc Clin Oncol. 2009;27:672–80.
12. Dotan E, et al. A phase II study of capecitabine, oxaliplatin, and cetuximab with or without bevacizumab as frontline therapy for metastatic colorectal cancer. A Fox Chase extramural research study. J Gastrointest Cancer. 2012;43:562–9.
13. Li X, Wang M, Liu G-Y, Ma J-L. Dual VEGF/EGFR inhibition versus single targeted agent treatment in patients with metastatic colorectal cancer: a meta-analysis of randomized trials. Int J Color Dis. 2016;31:1655–6.
14.•• Schwartzberg LS, 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 Off J Am Soc Clin Oncol. 2014;32:2240–7. **This manuscript reports results of the PEAK trial, one of the three clinical trials to compare anti-VEGF and anti-EGFR therapy head-to-head in the first-line setting.**
15.•• Heinemann V, et al. FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment for patients with metastatic colorectal cancer (FIRE-3): a randomised, open-label, phase 3 trial. Lancet Oncol. 2014;15:1065–75. **This manuscript reports results of the FIRE-3 trial, one of the three clinical trials to compare anti-VEGF and anti-EGFR therapy head-to-head in the first-line setting.**
16. Stintzing S, et al. FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab for metastatic colorectal cancer (FIRE-3): a post-hoc analysis of tumour dynamics in the final RAS wild-type subgroup

of this randomised open-label phase 3 trial. Lancet Oncol. 2016;17: 1426–34.
17. Modest DP, 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 Off J Am Soc Clin Oncol. 2015;33:3718–26.
18.•• Venook AP, Niedzwiecki D, Lenz HJ, et al. CALGB/SWOG 80405: Phase III trial of irinotecan/5-FU/leucovorin (FOLFIRI) or oxaliplatin/5-FU/leucovorin (mFOLFOX6) with bevacizumab (BV) or cetuximab (CET) for patients (pts) with KRAS wild-type (wt) untreated metastatic adenocarcinoma of the colon or rectum (MCRC). J Clin Oncol 2014;32(5s (suppl; abstr LBA3)). **This presentation reports results of the PEAK trial, one of the three clinical trials to compare anti-VEGF and anti-EGFR therapy head-to-head in the first-line setting.**
19. Lenz, H.-J. CALGB/SWOG 80405: Phase III trial of FOLFIRI or mFOLFOX6 with bevacizumab or cetuximab for patients with expanded RAS analyses in untreated metastatic adenocarcinoma of the colon or rectum. (2014).
20. Khattak MA, Martin H, Davidson A, Phillips M. Role of first-line anti-epidermal growth factor receptor therapy compared with anti-vascular endothelial growth factor therapy in advanced colorectal cancer: a meta-analysis of randomized clinical trials. Clin Colorectal Cancer. 2015;14:81–90.
21. Heinemann V, et al. A study-level meta-analysis of efficacy data from head-to-head first-line trials of epidermal growth factor receptor inhibitors versus bevacizumab in patients with RAS wild-type metastatic colorectal cancer. Eur J Cancer Oxf Engl. 2016;1990(67):11–20.
22. Wang H, et al. Efficacy and safety of anti-epidermal growth factor receptor therapy compared with anti-vascular endothelial growth factor therapy for metastatic colorectal cancer in first-line and second-line therapies: a meta-analysis. OncoTargets Ther. 2016;9: 5405–16.
23. Pietrantonio F, et al. First-line anti-EGFR monoclonal antibodies in panRAS wild-type metastatic colorectal cancer: a systematic review and meta-analysis. Crit Rev Oncol Hematol. 2015;96:156–66.
24.• Kumachev A, et al. A systematic review and network meta-analysis of biologic agents in the first line setting for advanced colorectal cancer. PLoS One. 2015;10:e0140187. **This manuscript, including both a direct meta-analysis of the PEAK, FIRE-3, and CALGB/SWOG 80405 studies and a network meta-analysis incorporating other first-line trials of anti-VEGF or anti-EGFR therapy, is the most comprehensive synthesis to date of all available data informing the choice between these two drug classes.**
25. Schrag, D. The relationship between primary tumor sidedness and prognosis in colorectal cancer.
26.• Venook, A. Impact of primary (1^{o}) tumor location on overall survival (OS) and progression-free survival (PFS) in patients (pts) with metastatic colorectal cancer (mCRC): Analysis of CALGB/SWOG 80405 (Alliance). **A retrospective analysis of CALGB/SWOG 80405 data with respect to tumor primary site location, this report was the first to highlight the importance of tumor location for the efficacy of anti-EGFR therapy.**
27.• Tejpar S, et al. Prognostic and predictive relevance of primary tumor location in patients with RAS wild-type metastatic colorectal cancer: retrospective analyses of the CRYSTAL and FIRE-3 trials. JAMA Oncol. 2016; doi:10.1001/jamaoncol.2016.3797. **This manuscript added further evidence to support the finding of limited benefit of anti-EGFR in right-sided tumors.**
28.•• Holch JW, Ricard I, Stintzing S, Modest DP, Heinemann V. The relevance of primary tumour location in patients with metastatic colorectal cancer: a meta-analysis of first-line clinical trials. Eur J Cancer Oxf Engl. 2017;70:87–98. **Including all relevant trials, this meta-analysis is the most comprehensive assessment to date of the impact of primary tumor location on efficacy of anti-VEGF and anti-EGFR therapies.**
29. Yamauchi M, et al. Colorectal cancer: a tale of two sides or a continuum? Gut. 2012;61:794–7.
30. Lee MS, et al. Association of CpG island methylator phenotype and EREG/AREG methylation and expression in colorectal cancer. Br J Cancer. 2016;114:1352–61.
31. Viloria-Petit A, et al. Acquired resistance to the antitumor effect of epidermal growth factor receptor-blocking antibodies in vivo: a role for altered tumor angiogenesis. Cancer Res. 2001;61:5090–101.