ABSTRACT

The 19th annual Western Canadian Gastrointestinal Cancer Consensus Conference (wCGCCC) was held in Winnipeg, Manitoba, 29–30 September 2017. The wCGCCC is an interactive multidisciplinary conference attended by health care professionals from across Western Canada (British Columbia, Alberta, Saskatchewan, and Manitoba) who are involved in the care of patients with gastrointestinal cancer. Surgical, medical, and radiation oncologists; pathologists; radiologists; and allied health care professionals participated in presentation and discussion sessions for the purpose of developing the recommendations presented here. This consensus statement addresses current issues in the management of colorectal cancer.

Key Words Colorectal cancer, adjuvant chemotherapy, surgery, molecular tests, immunotherapy, radioembolization, sidedness

Basis of Recommendations

The recommendations are based on presentation and discussion of the best available evidence. Where applicable, references are cited.

QUESTION 1

What is the optimal duration of oxaliplatin-based adjuvant chemotherapy in node-positive colon cancer?

Recommendations

■ For T1–3N1 disease, 3 months of capecitabine and oxaliplatin (CAPOX) treatment is a reasonable option. If using 5-fluorouracil (5FU), leucovorin, and oxaliplatin (FOLFOX), 6 months should remain the standard.

■ In “high risk” stage III (T4 or N2 disease), 6 months of oxaliplatin-based treatment is the standard of care.

Summary of Evidence

Treatment with 6 months of fluoropyrimidine–oxaliplatin has been the standard adjuvant treatment for stage III colon cancer.
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|-----------------------|---------------------------------|----------------------------------------------|
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| Dupré, Marc           | Pathologist                     | Diagnostic Services Manitoba                 |
| Gill, Sharlene        | Medical oncologist              | BC Cancer                                    |
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cancer since the landmark mosaic trial showed that the addition of oxaliplatin to 5FU improved 3-year disease-free survival (DFS) and 10-year overall survival (OS) . However, oxaliplatin is associated with cumulative dose-dependent neurotoxicity. Nearly all patients experience some degree of peripheral neuropathy during treatment, which can lead to functional impairment in nearly 45% of patients (31.4% grade 2 and 12.5% grade 3). Peripheral neuropathy can persist long after treatment is complete and in many cases can be permanent, with 30% of patients continuing to experience neuropathy 12 months after completion of adjuvant therapy.

The International Duration Evaluation of Adjuvant Chemotherapy (IDEA) collaboration was designed to assess whether, to minimize toxicity, the duration of oxaliplatin-based adjuvant chemotherapy could be reduced to 3 months from 6 months without compromising treatment efficacy. A prospectively planned pooled analysis, IDEA considered six concurrent international trials involving 12,834 patients, including Tosca, Scot, IDEA France, Horg, C80702, and Achieve. The primary endpoint was the noninferiority of 3 months compared with 6 months of oxaliplatin-based adjuvant chemotherapy (CAPOX or FOLFOX) in stage III colon cancer, with an upper-bound noninferiority margin of 12% for DFS (HR: 1.12). All stage III colon cancer patients randomized in the trials were included in the primary analysis, but several of the trials included a second randomization to address additional research questions. For example, the Alliance C80702 trial included a randomization to compare celecoxib with placebo after completion of FOLFOX, and the Tosca trial had a secondary randomization to bevacizumab, which was eventually dropped. In addition, some trials included stage II patients (Tosca, Scot, and Horg), and Scot also included rectal cancers, although the primary analysis focused on patients with stage III colon cancer.

At the American Society of Clinical Oncology 2017 annual general meeting, the primary analysis of the IDEA collaboration was shown to be negative because the upper bounds of the confidence interval passed the acceptable pre-specified noninferiority margin (DFS HR: 1.07; 95% CI: 1.00 to 1.15). The 3-year DFS was 74.6% for the 3-month course compared with 75.5% for the 6-month course. Depending on treatment received (CAPOX or FOLFOX), grade 2 or greater peripheral neuropathy was reduced to 15%–17% for 3 months of therapy compared with 45%–58% for 6 months of therapy (p < 0.001).

The IDEA collaboration included multiple pre-planned subgroup analyses. Specifically, the authors planned to assess subgroups stratified by N stage, T stage, chemotherapy regimen (FOLFOX vs. CAPOX), age (<70 years vs. >70 years), and tumour sidedness. When comparing outcomes based on regimen, patients who received FOLFOX did not meet the cut-off for noninferiority (HR: 1.16; 95% CI: 1.06 to 1.26); those who received CAPOX did (HR: 0.95; 95% CI: 0.85 to 1.06). The difference in outcome based on regimen was confirmed with an interaction test (p = 0.0051). Those results were driven largely by the Scot trial, which contributed more than half the CAPOX-treated patients to the full analysis and which also met its primary endpoint of demonstrating that 3 months of adjuvant oxaliplatin-based therapy was noninferior to 6 months of therapy (HR: 1.006; 95% CI: 0.909 to 1.114; p = 0.012).

Since the presentation of those data, there has been debate about how to interpret the stratification based on treatment regimen given that patients were not randomized according to type of chemotherapy. There was no suggestion that the patients who received CAPOX had more favourable baseline or disease characteristics. The increased efficacy of a capecitabine-containing regimen might be related to the continuous administration of capecitabine for 2 of 3 weeks, to the earlier exposure to higher doses of oxaliplatin, or perhaps to something inherent to the pharmacology of capecitabine.

Similarly, in the ACT trial, adjuvant capecitabine and 5FU were shown to be equivalent for DFS (p < 0.0001) and OS (p = 0.0001), but a trend toward superiority for capecitabine was observed for both endpoints (p = 0.068 and p = 0.060 respectively). Other data suggest that 3 months of continuous exposure to 5FU is superior to 6 months of bolus 5FU, and retrospective data suggest that CAPOX might be more active than FOLFOX in stage III colon cancer.

With respect to the subgroup analyses based on T and N stage, no single T or N stage met the noninferiority criteria; however, the authors of the IDEA collaboration performed an unplanned analysis of low-risk (T1–N3N1) compared with high-risk (T4 or N2) groups. In that analysis, which pooled the CAPOX and FOLFOX groups, the result in the low-risk group met the criteria for noninferiority (HR: 1.01; 95% CI: 0.90 to 1.12), but the result in the high-risk group was clearly inferior (HR: 1.12; 95% CI: 1.03 to 1.23). When the authors assessed those risk groups stratified by type of chemotherapy, neither CAPOX nor FOLFOX was noninferior in the high-risk group. In the low-risk group, CAPOX (HR: 0.85; 95% CI: 0.71 to 1.01), but not FOLFOX (HR: 1.10; 95% CI: 0.96 to 1.26), was noninferior. The statistical plan for the trial did not include those low- and high-risk groups as part of the pre-specified analysis, and so the post hoc nature of those results should be interpreted with caution. The large sample size and pragmatic nature of the groupings do, however, provide support for the interpretation.

Taking into account all the evidence, the results of the IDEA pooled analysis support a risk-based approach to patients with node-positive colon cancer. For patients with high-risk disease (T4 or N2), 6 months of oxaliplatin-based adjuvant therapy remains the standard of care. For patients with low-risk disease (T1–N3N1), 3 months of adjuvant CAPOX treatment is a reasonable option to consider. If using FOLFOX, 6 months of therapy remains the standard of care for all risk groups.

**QUESTION 2**

What is the optimal timing of surgery after neoadjuvant chemoradiation therapy in patients with clinical stage II or III rectal cancer?

**Recommendations**

- The optimal timing of surgery after neoadjuvant chemoradiation therapy in patients with clinical stage II and III rectal cancer is not known.
Surgery should be considered between 6 and 10 weeks after completion of chemoradiation in patients with clinical stage II or III rectal cancer.

Summary of Evidence
In the German rectal cancer study that demonstrated a benefit with neoadjuvant chemoradiation, surgery took place 6 weeks after completion of the chemoradiation. However, studies have suggested that a pathologic complete response (pCR) after neoadjuvant chemoradiation is associated with improved dsR and os. A recent meta-analysis suggested that increasing the interval between completion of neoadjuvant chemoradiation and surgery to more than 6–8 weeks significantly increased the rate of pCR without any increase in detrimental outcomes. Since publication of that meta-analysis, other large retrospective series have also demonstrated an increase in pCR rates with a longer interval from completion of chemoradiation to surgery. Peak pCR rates were seen when surgery occurred between 9 and 12 weeks after completion of neoadjuvant therapy, although one study noted an increase in circumferential radial margin involvement if surgery occurred more than 12 weeks after completion of the chemoradiotherapy.

The GRECCAR-6 trial is the only prospective randomized controlled trial that was designed to evaluate the pCR rate with an increased interval between completion of neoadjuvant therapy and definitive surgery. That multicentre trial randomized patients with clinical T3–4 or Tx node-positive tumours of the mid- or lower rectum to surgery either 7 or 11 weeks after completion of neoadjuvant chemoradiation. No difference in the primary endpoint of pCR was observed between the two groups (15.0% in the 7-week group vs. 17.4% in the 11-week group, p = 0.5983). In both groups, the pCR rate was as high or higher than the pCR rates reported in retrospective studies. In terms of secondary outcomes, complete total mesorectal excision specimens were obtained more often in the 7-week group (90% vs. 79%, p = 0.0156). Although no difference in anastomotic complications was observed, differences in medical complications were evident, mostly because of more urinary complications in the 11-week group.

A longer wait time between completion of neoadjuvant chemoradiation and surgery was not associated with an increase in synchronous metastatic disease (2.3% in the 7-week group vs. 1.5% in the 11-week group, p = 1.00). The results of the study suggest that waiting longer between the completion of neoadjuvant therapy and surgery is not associated with an improvement the pCR rate and might be associated with increased morbidity; however, the results are far from indisputable. The optimal timing for surgery after completion of neoadjuvant chemoradiation for stages II and III rectal cancer remains unclear. Based on the data, surgery should be considered between 6 and 10 weeks after completion of chemoradiation.

**QUESTION 3**

What is the current role for nonsurgical management of rectal cancer after a complete clinical response (cCR) to neoadjuvant chemoradiation therapy?

**Recommendations**
- The standard approach for patients after a cCR is definitive surgical resection.
- If being considered for a nonsurgical approach, patients should be considered for a clinical trial if available.
- In patients who do not undergo resection, an intensive surveillance strategy is required. The case must be presented at a multidisciplinary case conference.
tumour found on pathology examination\textsuperscript{19}. Currently no imaging modality has been shown to reliably predict pCR\textsuperscript{20–33}. Also, in patients who do not undergo standard surgical resection, there is a possibility that curative surgery might not be an option upon recurrence\textsuperscript{34}. Although the data for non-operative management is promising, prospective clinical trials are necessary before such an approach can be recommended in patients who experience a ccr in response to neoadjuvant chemotherapy. The results of the prospective NCT01047969 trial (https://clinicaltrials.gov/ct2/show/NCT01047969) will add further information. For now, surgical resection remains the standard of care. If a patient declines surgical intervention or is medically unfit for major surgery, their case should be discussed in a multidisciplinary case conference. Ideally, non-operative approaches should occur in the setting of a prospective clinical trial, if available. In patients who opt for a nonsurgical approach, close and frequent monitoring should occur. No guidelines discussing how to follow those patients have been published; however, an intensive surveillance strategy should include frequent history, physical examination, endoscopy, and cross-sectional imaging (computed tomography and magnetic resonance imaging).

**QUESTION 4**

What molecular tests should now be the standard of care for patients with newly diagnosed crc?

**Recommendations**

- Mismatch repair (MMR) testing should be performed in all CRC patients for Lynch syndrome ascertainment and for predictive and prognostic factors.
- Extended RAS and BRAF testing should be performed in patients with metastatic disease being considered for therapy.
- Other biomarkers currently remain investigational.

**Summary of Evidence**

In CRC, molecular testing can inform tumour classification, pathogenesis, prognosis, and prediction of response to specific therapies. Tumour mismatch repair (MMR) protein status, microsatellite instability (MSI) status, and BRAF and KRA$S$/NRAS mutation status are the most commonly sought molecular tests for CRC.

Testing for MMR allows for the identification of MMR-deficient (dMMR) CRC, either hereditary (Lynch syndrome secondary to germline mutations) or sporadic in nature. In CRC, dMMR produces MSI through DNA replication errors, and MSI-high (MSI-H) CRCs are associated with improved pFS and OS\textsuperscript{35}. Unlike Lynch syndrome-associated CRC, sporadic dMMR tumours are associated with BRAFV600E mutations and typically present as right-sided tumours in older female patients\textsuperscript{36,37}. Although clinical features and some tumour morphology features can help to identify dMMR and MSI-H tumours, those approaches lack sensitivity. Immunohistochemical (IHC) testing for MMR expression has become widespread in recent years and is currently used primarily for screening for Lynch syndrome. The standard 4-antibody MMR IHC panel incorporates MLH1, MSH2, MSH6, and PMS2 testing and has sensitivity and specificity exceeding 90\% for the detection of dMMR tumours\textsuperscript{38}. Mismatch repair IHC testing is highly concordant with polymerase chain reaction–based MSI testing\textsuperscript{38,39}.

In select cases of early-stage CRC, MMR status can provide information that assists in decision-making for adjuvant chemotherapy. Retrospective analyses suggest that single-agent fluoropyrimidine therapy might be ineffective in dMMR or MSI-H CRCs\textsuperscript{40–42}. MMR or MSI status could therefore influence whether adjuvant therapy consists of observation alone, single-agent fluoropyrimidine therapy, or oxaliplatin-based doublet chemotherapy after surgical resection for stage II colon cancers. Furthermore, recent data suggest that MMR and MSI status can identify patients with metastatic CRC who might benefit from immunotherapy (see Question 5).

Selective, aged-based MMR testing is advocated as a cost-effective process for Lynch syndrome screening, but only universal testing is able detect all sporadic dMMR or MSI-H cancers\textsuperscript{43}. Testing for MMR is therefore recommended in all patients with CRC, because it helps to identify Lynch syndrome and provides prognostic\textsuperscript{44} and predictive information.

In CRC, BRAFV600E mutations are common; they are identified in approximately 10\% of all CRCs, 60\% of sporadic dMMR tumours, and approximately 8\% of advanced CRCs\textsuperscript{45–48}. A BRAF V600E mutation in metastatic CRC is associated with worse progression-free survival (PFS) and OS, and a decreased response to anti-EGFR agents\textsuperscript{46,47,49,50}. More than half of all CRC harbour mutations in KRA$S$, NRAS, and BRAF; only a small proportion of CRCs have mutations in both RAS and RAF\textsuperscript{51}. Improved PFS and OS are expected for patients with wild-type (wt) KRA$S$ and BRAF metastatic CRCs treated with EGFR-targeted therapies\textsuperscript{52}.

In the setting of MMR–deficient tumours, the presence of a BRAF mutation excludes a Lynch syndrome–related cancer\textsuperscript{44}. Testing for BRAFV600E and KRA$S$ mutations can be performed by polymerase chain reaction. Recently, nuc clones that detect the BRAF V600E protein product have become commercially available. When fully optimized, nuc with the VE1 clone has sensitivity and specificity exceeding 90\% for the detection of the BRAFV600E protein product\textsuperscript{52}.

Because the tests provide information about response to anti-EGFR therapies and screen for Lynch syndrome, it is recommended that patients with metastatic CRC undergo testing for KRA$S$/NRAS and BRAF\textsuperscript{44}. Other biomarkers remain investigational at this point in time.

**QUESTION 5**

What is the role of immunotherapy in patients with metastatic CRC?

**Recommendations**

- Use of a PD-1 inhibitor (nivolumab or pembrolizumab) is a reasonable option in patients with stage IV MSI-H or MMR-deficient CRC after treatment failure with, or intolerance to, fluoropyrimidine, oxaliplatin, and irinotecan.
- In MMR-proficient tumours, single-agent nivolumab or pembrolizumab has been shown to be ineffective and should not be used.
Summary of Evidence
The distinct subset of msi-H crcs is distinguished by a hypermutable state, increased neoantigen load, and tumour-infiltrating lymphocytes. Although such tumours constitute only 3%–4% of all metastatic crcs, the foregoing characteristics suggest that they might respond to checkpoint inhibitors.

In 10 patients with dmmr crcs, Le et al.53 demonstrated that the PD-1 inhibitor pembrolizumab resulted in an overall response rate (orr) of 40% and a disease control rate (dcr) of 90%. Responses tended to be quick and prolonged. Pembrolizumab was well tolerated, with few grade 3 or 4 toxicities reported. In patients with mmr-proficient tumours, the response rate was 0%. Those results were confirmed in the KEYNOTE-164 study, which showed an orr of 28% and a dcr of 51% in 61 patients with msi-H tumours treated with pembrolizumab54,55.

The PD-1 inhibitor nivolumab has also shown promising activity. The CheckMate 142 study was a nonrandomized phase ii trial of nivolumab in heavily pretreated patients with msi-H crc56. Patients in the first arm received nivolumab 3 mg/kg every 2 weeks, and patients in the second arm received a combination of nivolumab 3 mg/kg plus ipilimumab 1 mg/kg every 3 weeks for 4 cycles, followed by nivolumab 3 mg/kg every 2 weeks until progression. In the 74 patients who received nivolumab monotherapy, the orr and dcr were 36% and 74% respectively56. The therapy was well-tolerated, with low grade 3 or 4 toxicities. Recently, the results of the combination therapy arm were published, showing an impressive 55% orr and 88% dcr57. Grade 3 or 4 toxicities occurred in 32% of patients, with diarrhea, fatigue, and pruritus being the most frequent adverse events reported. The response rates with combination immunotherapy appear to be higher, but because of the nonrandomized nature of the trial, a direct comparison between the two arms is not possible.

In 2017, pembrolizumab and nivolumab were both approved by the U.S. Food and Drug Administration for patients with msi-H or dmmr metastatic crc experiencing progression after treatment with a fluoropyrimidine, oxaliplatin, and irinotecan. At the time of the present review, no ircc Notice of Compliance had been issued for pembrolizumab or nivolumab in this setting.

To summarize, a small (3%–4%) subset of crc patients appears to derive substantial benefit from checkpoint inhibitors. The benefits are marked and therefore PD-1 inhibitors should be offered to this select group of patients.

QUESTION 6

What are the indications for radioembolization in patients with metastatic crc?

Recommendations

There is no survival benefit with the use of radioembolization in patients with metastatic crc, and its use should not be considered in the first-line setting unless part of a clinical trial.

Summary of Evidence
The prognosis of patients with crc and liver metastasis is determined largely by the degree of liver infiltration by tumour. The rationale for, and use of, liver-directed therapies such as surgical resection or ablation for the treatment of resectable or potentially locally curative liver metastases was, despite high rates of recurrence within the liver, established in population-based cohorts and randomized controlled trials58,59. A recent randomized phase ii trial of patients with crc and unresectable liver-limited metastases revealed that, at a median follow-up of 9.7 years, compared with chemotherapy alone, chemotherapy plus locoregional treatment with radiofrequency ablation, with or without resection, achieved a significant improvement in os (HR: 0.58; 95% CI: 0.38 to 0.88, p < 0.01)60. However, that study had methodology limitations that make the results difficult to interpret. The study was initially designed as a phase iii trial, with os as the primary endpoint. But accrual was slower than expected, and the study was amended to a phase ii trial with a smaller sample size and a primary endpoint of a 30-month os rate exceeding 38% in the combined-modality arm. Secondary endpoints included PFS and os. At the time of the initial report, a statistically significant difference in PFS was observed between the two arms (16.8 months for patients in the combined-modality arm vs. 9.9 months in the chemotherapy-only arm, p = 0.025), but no difference in os61. Systemic treatment initially consisted of folfox4. After 2005, bevacizumab was added, and in both arms, according to protocol, chemotherapy was required to be given for 6 months only. Although the results are encouraging, the study sample consisted of highly selected patients who experienced an impressive median os in both groups (45.6 months for the combined-modality group vs. 40.5 months in the chemotherapy-only arm), and the use of locoregional therapies in patients with incurable crc remains unclear.

The use of selective internal radiation therapy (sirt) that uses resin-coated microspheres loaded with the therapeutic radioisotope yttrium-90 has demonstrated encouraging results in terms of dcr62 and depth of response62,63. Those results have been reiterated in small studies in the third line or in chemorefractory disease64, in the second line65, and in the earlier first line66 for patients with liver-dominant metastatic crc. The sirtfox and foxfire family of studies was designed as a series of multinational trials to determine whether, compared with systemic chemotherapy alone, radioembolization with yttrium-90 resin microspheres (sir-Spheres: Sirtex Medical, Sydney, Australia) in combination with systemic chemotherapy resulted in an improvement in os in the first-line treatment of patients with metastatic crc with unresectable liver metastases67. Despite a higher proportion of patients achieving a tumour response and improved liver-specific PFS, the aggregated studies failed to achieve the primary outcome of improvement in os with the addition of sirt to chemotherapy (HR: 1.04; 95% CI: 0.90 to 1.19; p = 0.61). The groups showed no difference in overall PFS or the rate of conversion to a surgically resectable scenario. Notably, rates of conversion to surgical resection were lower than expected in both arms, possibly related to the high incidence of an intact primary (17% in the sirt-plus-chemotherapy arm vs. 16% in the chemotherapy-only arm) and the presence of extrahepatic metastatic disease63. The most common grade 3 or
4 adverse event was neutropenia, which occurred in 37% of patients who received sunitinib plus chemotherapy and in 24% of patients who received only chemotherapy. Increased rates of thrombocytopenia, abdominal pain, and fatigue were also seen with sunitinib plus chemotherapy compared with chemotherapy alone. Technical considerations related to the radioactivity dosing schema, biomarkers, catheter placement, and site of actual administration were not fully explored; however, by nature, the sunitinib procedure requires a high degree of technical expertise. Adverse events of gastrointestinal toxicities might have been attributable to a lack of experience on the part of the interventional radiologists performing the procedure in an earlier phase of the study, with no roll-in period.

A post hoc analysis of the SIRFLOX and FOXX-10 studies suggests that patients with right-sided primary tumours experienced an os benefit with sunitinib plus chemotherapy compared with chemotherapy alone (median os: 22 months vs. 17 months). The presence of a right-sided primary has been associated with worse prognosis and therefore warrants further investigation.

Based on the data, the addition of sunitinib to chemotherapy in the first-line treatment of unselected patients with metastatic cancer is not recommended. Outside of a clinical trial setting, sunitinib should not be used in the first-line setting of metastatic cancer with liver metastases. If sunitinib is being considered in the chemotherapy-refractory setting, the patient’s case should be discussed in a multidisciplinary case conference setting.

**QUESTION 7**

Does sidedness matter in advanced colon cancer?

**Recommendations**

- Right-sided tumours are genomically different from left-sided tumours. That difference can affect the use of biologic and chemotherapy strategies. Prognosis is poorer in right-sided tumours, which might not respond well to EGFR-directed therapies.

**Summary of Evidence**

Cancers of the right side of the colon (cecum, ascending colon, hepatic flexure, and transverse colon) differ on a molecular level from cancers of the left side of the colon (splenic flexure, and descending and sigmoid colon). The molecular differences between right- and left-sided CRCs might be related to their different embryologic origins, given that the right colon originates from the midgut, and the left colon develops from the hindgut.

It is possible that tumour location is simply a marker for molecular biology. BRAF and KRAS mutations and hypermethylation occur more commonly in right-sided tumours; left-sided tumours are more likely to be non-mutated. Gene expression profiling has led to the identification of 4 consensus molecular subtypes (CMS) of CRC:

- CMS1 tumours tend to display MSI, CpG island methylator phenotype, hypermethylation, and BRAF mutation.
- CMS2 (canonical type) tumours have high somatic copy number alterations and Wnt and Myc activation.
- CMS3 tumours have low CpG island methylator phenotype and somatic copy number alterations, together with mixed MSI status.
- CMS4 (mesenchymal type) tumours are associated with high somatic copy number alterations, angiogenesis, stromal infiltration, and activation of transforming growth factor β.

The CMS type appears to be associated with tumour location and prognosis. The CMS1 type tends to occur more frequently in women with right-sided tumours and is associated with worse prognosis upon relapse. In contrast, CMS2 tumours tend to be left-sided and associated with better prognosis. The CMS4 tumours are associated with worse relapse-free survival and OS.

Retrospective analyses of randomized clinical trials confirm that tumour sidedness is associated with prognosis, even in RAS wt tumours. Among the 370 patients from the CRYSTAL and FIRE-3 trials who had RAS wt metastatic CRC, FFS and OS were superior for the patients with left-sided tumours compared with the patients with right-sided tumours, although the number of patients with right-sided tumours was small in both studies (33 and 28 respectively). A number of other retrospective analyses support the finding that tumour sidedness is prognostic.

Furthermore, recent data suggest that tumour sidedness might be predictive, because patients with RAS wt left-sided tumours experience superior survival when an EGFR-directed antibody is added to chemotherapy. The Cancer and Leukaemia Group B/SWOG 80405 study compared the addition of cetuximab or bevacizumab to 5FU-based chemotherapy, showing no difference in median OS (30 months with chemotherapy–cetuximab vs. 29 months with chemotherapy–bevacizumab; HR: 0.98; 95% CI: 0.77 to 1.24; p = 0.72). However, when the data were retrospectively examined to assess the effect of primary tumour location in patients with RAS wt, those with left-sided tumours experienced a greater OS benefit from chemotherapy–cetuximab than from chemotherapy–bevacizumab (median OS: 36 months vs. 31.4 months), and those with right-sided tumours experienced better survival with chemotherapy–bevacizumab than with chemotherapy–cetuximab (median survival: 24.2 months vs. 16.7 months). A meta-analysis of randomized controlled trials has since confirmed that, in patients with RAS wt left-sided colon cancer, survival is improved with the use of EGFR-directed therapy plus chemotherapy compared with the use of bevacizumab plus chemotherapy. In contrast, patients with right-sided colon cancer do not receive the same benefit from EGFR-directed therapy and seem to do better with chemotherapy–bevacizumab. Although results have consistently suggested that tumour sidedness is predictive of response to EGFR-directed therapy plus chemotherapy, the analyses have all been retrospective in nature and should be interpreted with caution. Prospective data are eagerly awaited.

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CONFLICT of INTEREST DISCLOSURES
We have read and understood Current Oncology’s policy on disclosing conflicts of interest, and we declare the following interests: CAK has received research grants from Celgene and is a co-investigator on trials with Pfizer and Novartis. HL has received honoraria for serving on advisory boards for Eisai, Taiho, Roche, Lilly, Amgen, and Leo Pharma, and is an investigator on trials as a site principal investigator or co-investigator with Bayer, Bristol–Myers Squibb, Lilly, Roche, AstraZeneca, and Amgen. The remaining authors declare that they have no conflicts to disclose.

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