News & Views

Research Highlights

Highlights from the latest articles in targeted anticancer therapy

Is dual antibody therapy with chemotherapy for metastatic colorectal cancer ready for prime time?

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Evaluation of: Tol J, Koopman M, Cats A *et al.*: Chemotherapy, bevacizumab, and cetuximab in metastatic colorectal cancer. *N. Engl. J. Med.* 360, 563–572 (2009);

Hecht JR, Mitchell E, Chidiac T *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.* 27, 672–680 (2009).

Great advances have been made in the past 10 years in the management of metastatic colorectal cancer (MCC). Median overall survival has improved from approximately 6 months with best supportive care, to 10–12 months with 5FU monotherapy, to more than 20 months with current regimens. Much of this progress stems from the addition of new cytotoxic and biologic agents to the medical oncologist's armamentarium. Currently, the most active agents against MCC include cytotoxics (fluoropyrimidines, oxaliplatin, and irinotecan) and biologics (EGFR inhibitors such as cetuximab and panitumumab, and VEGF inhibitors such as bevacizumab).

Numerous studies demonstrate that combining cytotoxic chemotherapy agents improves clinical outcomes. Overall survival, for instance, with 5FU/LV is estimated at 12 months, whereas doublet combinations with 5FU/LV plus oxaliplatin have resulted in survival rates of 16 months [1,2]. Other trials demonstrate an even greater improvement in overall survival with the addition of bevacizumab to irinotecan- or oxaliplatin-based doublets [3]. Based on these observations, bevacizumab plus chemotherapy represents a standard of care for the first-line treatment of MCC. By contrast, there is no direct evidence demonstrating whether cetuximab in combination with irinotecan improves overall survival in comparison with best supportive care or oxaliplatin/5FU/LV, although the evidence on tumor response rate suggests that cetuximab plus irinotecan has some clinical activity.

Given the improvements seen with the use of multiple cytotoxic treatments, in addition to the benefit seen with adding bevacizumab, it was logical to ask whether adding yet another targeted agent (an anti-EGFR, such as cetuximab or panitumumab) might improve outcomes even more.

CApecitabine, IRinotecan, Oxaliplatin-2 (CAIRO-2) and Panitumumab Advanced Colorectal Cancer Evaluation (PACCE) are two recently published randomized Phase III trials aimed at addressing the role of dual antibody therapy as first-line treatment for MCC. CAIRO-2 was a multi-institutional Phase III trial of 732 patients conducted in the Netherlands, where patients with previously untreated MCC were randomized to receive capecitabine, oxaliplatin and bevacizumab with or without cetuximab every 3 weeks [4]. Tumor response was evaluated every 9 weeks and the primary end point of the study was progression-free survival. After a median follow-up of 23 months, the arm that received cetuximab had a worse median progression-free survival (9.4 months vs 10.7 months, $p = 0.01$), but similar median overall survival (19.4 months vs 20.3 months, $p = 0.16$). A total of 528 patients (71%) had *KRAS* gene mutation status tested and 206

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(39.6%) had an activating *KRAS* mutation. Cetuximab-treated patients with mutated *KRAS* had significantly worse progression-free survival (8.1 months vs 10.5 months, p = 0.04) and overall survival (17.2 months vs 24.9 months, p = 0.03) compared with patients with wild-type *KRAS* tumors. There was no significant difference in progression-free survival between patients treated with or without cetuximab with wild-type *KRAS* tumors. There were significantly more grade 3 or 4 adverse events in the group receiving cetuximab (81.7 vs 73.2%, p = 0.006), with cutaneous events, diarrhea, fatigue and hypertension being the most common.

PACCE was a multicenter Phase III trial conducted in the USA for previously untreated MCC patients who were randomized to bevacizumab and chemotherapy with or without panitumumab every 2 weeks [5]. Per investigator choice, patients could receive oxaliplatin- or irinotecan-based cytotoxic treatment, with dose and scheduling left to the physician's discretion. Capecitabine-containing regimens were excluded. The larger oxaliplatin-based cohort accrued 823 patients, with the primary end point of progression-free survival. Only 230 patients were accrued to the irinotecan group, with safety as the primary objective and all efficacy end points being descriptive given the cohort's small size. After one of multiple planned safety reviews, panitumumab was discontinued owing to decreased progression-free survival and increased toxicity in the panitumumab arm. In the final analysis, median progression-free survival (10.0 months vs 11.4 months; hazard ratio [HR]: 1.27) and overall survival (19.4 months vs 24.5 months; HR: 1.43) were worse in the panitumumab arm. *KRAS* mutation status was determined in 82% of tumor samples, with mutations found in 40%. In contrast to previous biomarker studies conducted with panitumumab, worse clinical outcomes were seen in both the wild-type and mutant *KRAS* groups treated with panitumumab. In addition, more patients experienced grade 3 or greater adverse events in the panitumumab arm compared with the control arm (90 vs 77%). The most commonly observed toxicities in the panitumumab arm included skin toxicity and diarrhea, along with dehydration, hypomagnesemia, infections and pulmonary embolism. Finally, patients in the panitumumab arm had less chemotherapy and bevacizumab delivered, as well as more frequent chemotherapy and/or antibody dose delays.

The reason for the observed detrimental effects with the addition of an anti-EGFR in this setting is not clear. Preclinical studies have demonstrated that VEGF and EGFR inhibitors can have additive effects and that combined inhibition is effective in EGFR-resistant cell lines. Some have criticized the statistical assumptions made in PACCE, believing that an estimated progression-free survival of 12 months in the control arm was optimistic compared with results from prior studies, including NO16966. This study, which compared two oxaliplatin-based regimens with or without bevacizumab, showed a median progression-free survival of 9.4 months for the bevacizumab arm [6]. Others have commented that allowing multiple different treatment schedules and tumor assessment every 12 weeks were flaws in PACCE's trial design. Perhaps more troubling than these findings is the fact that approximately two thirds of the patients discontinued treatment for reasons unrelated to disease progression, including toxicity. However, it is not clear that any of these observations explain the results, because the CAIRO-2 study had a conventional standard arm and study design (tumor evaluation was done every 9 weeks, and patients in both arms received similar dose intensity). It also appears that the detriment in progression-free survival was seen with either oxaliplatin- or irinotecan-based regimens. Finally, it is possible that there is an unexpected negative interaction between cytotoxic chemotherapy and VEGF and EGFR inhibitors. This needs to be investigated in preclinical models and in prospective future clinical trials.

CALGB 80405 is currently accruing previously untreated MCC patients to treatment, based on physician choice, with 5-fluorouracil, leucovorin and oxaliplatin (FOLFOX) or folinic acid, fluorouracil and irinotecan (FOLFIRI), and randomizing them to adding bevacizumab, cetuximab, or both. Results from this trial will provide more insight into whether dual antibody therapy is prudent or not. For now, it appears that this treatment should only be offered to patients enrolled on clinical trials.

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Biomarkers predict activity of anti-EGFR inhibitors in metastatic colorectal cancer

Evaluation of: Karapetis CS, Khambata-Ford S, Jonker DJ *et al.*: *K-ras* mutations and benefit from cetuximab in advanced colorectal cancer. *N. Engl. J. Med.* 359, 1757–1765 (2008).

Selecting the appropriate patients for treatment with targeted therapies is a major challenge in oncology. Cetuximab is a chimeric human/mouse monoclonal antibody that binds to EGFR and competitively inhibits ligand binding. When used as a single agent in advanced colorectal cancer patients who are either refractory or intolerant to standard chemotherapy, it leads to an improvement in overall survival compared with best supportive care (6.1 months vs 4.6 months) [1]. However, despite the fact that all patients enrolled on this study had tumors that were EGFR-positive by immunohistochemistry (IHC), only 8 and 31.4% of patients in the cetuximab arm had a partial response or stable disease, respectively. These data suggest that EGFR IHC staining may not be a relevant biomarker to predict cetuximab activity.

In a separate analysis of patients enrolled on this study, investigators hypothesized that *KRAS* mutation status might serve as a more useful biomarker, and thus studied the correlation between *KRAS* mutation and survival [2]. They were able to determine the *KRAS* mutation status of 68.9% (394 patients) of tumor samples, with 42.3% of patients having at least one mutation in exon 2 of the *KRAS* gene. Patients treated with cetuximab with wild-type *KRAS* had significantly improved median progression-free survival (3.7 vs 1.9 months, $p < 0.001$) and overall survival (9.5 vs 4.8 months, $p < 0.001$) compared with best supportive care. On the other hand, patients with *KRAS* mutations treated with cetuximab did not have significant differences in progression-free or overall survival compared with best supportive care. Finally, there are conflicting reports regarding whether *KRAS* mutation status is prognostic apart from EGFR pathway blockade, so the investigators examined overall survival in the best supportive care group and found that in this cohort, there was no correlation between survival and *KRAS* mutation status.

Among colorectal cancer cases, 75–82% are EGFR-positive by IHC, and no correlation between the presence or intensity of IHC staining and clinical response has been demonstrated [3]. The study by Karapetis *et al.* reviewed here gives clinicians a useful tool to help predict response to treatment with cetuximab. Similar results have been reported for patients on four other randomized trials that treated patients with either cetuximab or panitumumab, another EGFR inhibitor [4]. Based on these studies as well as five single-arm (Phase II) retrospective studies, the American Society of Clinical Oncology (ASCO) has issued provisional clinical guidelines. ASCO recommends that patients with "metastatic colorectal cancer who are candidates for anti-EGFR antibody therapy should have their tumor tested for *KRAS* mutations [and that] if *KRAS* mutation in codon 12 or 13 is detected, then patients with metastatic colorectal carcinoma should not receive anti-EGFR antibody therapy as part of their treatment" [4]. Additional biomarkers, including *BRAF* mutation status, may increase the value of the *KRAS* mutation determination to predict anti-EGFR drug activity [5].

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Bevacizumab for metastatic colorectal cancer: is longer better?

Evaluation of: Grothey A, Sugrue MM, Purdie DM *et al.*: Bevacizumab beyond first progression is associated with prolonged overall survival in metastatic colorectal cancer: results from a large observational cohort study (BRiTE). *J. Clin. Oncol.* 26, 5326–5334 (2008).

Bevacizumab is a humanized monoclonal antibody that binds to and neutralizes VEGF when added to first- and second-line chemotherapy for patients with metastatic colorectal cancer, and leads to improvements in both progression-free and overall survival [1,2]. Furthermore, preclinical studies show that sustained VEGF inhibition can lead to and maintain tumor regression. However, in the clinic, it is unclear whether patients benefit from continuing bevacizumab after they have developed progressive disease. The Bevacizumab Regimens investigation of Treatment Effects and safety (BRiTE) study is a large observational study of 1953 patients, involving 248 study sites in 49 US states, with previously untreated metastatic colorectal cancer treated with bevacizumab as part of first-line therapy [3]. Approximately 60% of patients received FOLFOX chemotherapy in combination. Patients had a progression-free survival of 10.0 months and median overall survival of 25.1 months. However, while the progression-free survival was consistent with that reported from recent randomized trials including bevacizumab, the median overall survival was longer than expected. This was particularly striking given that this was a community-based group of patients with a higher proportion of patients older than 65 years, a lower proportion of patients with ECOG performance status of 0, and a higher proportion receiving adjuvant chemotherapy compared with similar studies, including AVF2107 (irinotecan, 5FU, leucovorin with or without bevacizumab) [2]. This paper sought to determine pre- and post-treatment factors in BRiTE that could explain the discrepancy between progression-free and overall survival.

To accomplish this, investigators grouped the 1445 patients who experienced disease progression into three groups: those who did not go on to receive additional treatment (no post-progressive disease [PD] treatment, 253 patients), those who received additional treatment but no more bevacizumab (no bevacizumab beyond first progression [BBP], 531 patients), and those who received additional treatment with bevacizumab (BBP, 642 patients). Since only 19 patients received bevacizumab alone post-PD, this cohort was excluded from the analysis because it was too small to consider separately. The median overall survival for the no post-PD, no-BBP, and BBP groups was 12.6, 19.9 and 31.8 months, respectively. In multivariate analysis, BBP was independently and significantly associated with improved survival ($p < 0.001$), compared with no-BBP. The implication of this study is that after patients develop progressive disease, continuing bevacizumab while changing the chemotherapy may still positively affect patient outcome. As response rates are not reported in this analysis, we can not conclude whether bevacizumab is acting as a chemosensitizing agent for sequential chemotherapy administration or a cytostatic agent. However, a recent study conducted in metastatic renal cell carcinoma demonstrates that premature bevacizumab discontinuation can have a negative impact on survival [4].

While these results are intriguing, it is important to note that there are inherent biases in observational studies. This hypothesis should thus be tested in a prospective fashion prior to being adopted for routine clinical use. The mechanisms of action of bevacizumab are diverse and complex, and angiogenic escape pathways are not well understood. It has been hypothesized that modification of the chemotherapy regimen may expose endothelial cells to a different stress, while the anti-VEGF effect serves as a chemosensitizer to the tumor vasculature. Prospective clinical trials, including SWOG 0600, are currently evaluating the role of antiangiogenics beyond tumor progression.

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