Since the early 1990s, adjuvant chemotherapy has been the standard of care in patients with stage III and high-risk stage II colon cancer. Trials conducted with 5-fluorouracil (5-FU)-based therapy, initially combined with levamisole and later with leucovorin as a biomodulator, showed significant improvement in disease-free survival (DFS) and overall survival (OS) over earlier regimens (1, 2). A recent meta-analysis of nearly 21,000 patients included in randomized adjuvant trials in the 5-FU era clearly established 3-year DFS as a valid surrogate marker for 5-year OS (3). This finding, along with MOSAIC trial results showing improved DFS in early-stage colon cancer, however, is unclear. In addition, the long-term safety of biological agents in potentially surgically cured patients has not yet been established. This review discusses the potential caveats and concerns associated with the uncritical use of targeted agents as adjuvant therapy before their safety and efficacy in this setting has been indisputably established in definitive phase III trials.

**Abstract**

For nearly two decades, adjuvant chemotherapy has been the standard of care in patients with early-stage colon cancer at high risk of recurrence. Until now, treatment has been based on the use of cytotoxic drugs that have well-demonstrated efficacy in advanced colorectal cancer. Most recently, targeted biological agents [i.e., antibodies against the epidermal growth factor receptor and vascular endothelial growth factor] have become essential components of the palliative medical treatment of colorectal cancer. Proof of efficacy of these agents in advanced disease has led to the initiation of several trials testing epidermal growth factor receptor and vascular endothelial growth factor antibodies in the adjuvant setting. Although definitive results of ongoing adjuvant studies will not be available for 2 to 3 years, some oncologists might already inappropriately consider the use of these targeted agents as a component of adjuvant therapy in selected patients. Whether the results obtained in advanced colorectal cancer can be readily translated into a projected efficacy in early-stage colon cancer, however, is unclear. In addition, the long-term safety of biological agents in potentially surgically cured patients has not yet been established. This review discusses the potential caveats and concerns associated with the uncritical use of targeted agents as adjuvant therapy before their safety and efficacy in this setting has been indisputably established in definitive phase III trials.

**General Considerations for the Selection of Agents for Testing in the Adjuvant Setting**

The selection of agents for testing in the adjuvant setting is based on several criteria. In general, agents must have shown activity (at least in phase II and preferably in phase III trials) in advanced disease before being tested in the adjuvant setting. The basic goal of adjuvant therapy in this context is the eradication of micrometastasis as a prerequisite of long-term, tumor-free survival and cure. The response rate achieved in metastatic colorectal cancer (7, 8). Although definitive results of these studies will not be available for 2 to 3 years, some oncologists might already inappropriately consider the use of such targeted agents as a component of adjuvant therapy in selected patients.

This review discusses the potential implications of the use of targeted agents in the adjuvant setting and speculates about their efficacy in early-stage colon cancer.
depending on baseline risk, would have been cured by therapy; additionally, a substantial percentage of patients, will actually experience a treatment benefit with adjuvant EGFR agents (17, 18). select patients as candidates for adjuvant treatment with anti–epidermal growth factor receptor (EGFR) and anti–vascular endothelial growth factor (VEGF) therapy have yet to be validated in larger patient cohorts before they can be used to associate with trastuzumab, a monoclonal antibody that has successfully applied in patients with HER-2–positive breast cancer, in whom substantial improvement in DFS and OS was from which the relevant treatment effect of the adjuvant use of surgery alone. Thus, the safety and toxicity of a regimen used in the adjuvant setting deserves critical attention, especially with regard to potential long-term side effects. Late-onset toxicities and long-term consequences of cytotoxic chemotherapy have been well demonstrated in pediatric and adult oncology, but the long-term safety of targeted agents (e.g., VEGF and EGFR inhibitors) has not yet been established. Several decades of follow-up might be needed to fully realize the biological consequences of, for example, 12 months of VEGF blockade on the cardiovascular or neurologic system. Thus, it should be mandated that patients currently enrolled in adjuvant clinical trials with biological agents be registered in a long-term observational study to potentially discover delayed adverse events.

Targeted Agents with Proof of Efficacy in Colorectal Cancer

VEGF and EGFR antibodies have become standard components in the algorithms of medical therapy in advanced colorectal cancer and are currently undergoing clinical testing in early-stage colon and rectal cancer (refs. 7, 8; see Table 1). Although additional targeted agents (or combinations of biologies) may, in the future, show proof of efficacy and safety in advanced colorectal cancer and thus emerge as candidates for evaluation in the adjuvant setting, at present, only EGFR and VEGF inhibitors meet these criteria.

Bevacizumab

The anti-VEGF agent bevacizumab seems to have a rather indirect effect on malignant tumors and lacks substantial antitumor efficacy as a single agent (19). Its presumed mechanisms of action are the increased delivery of cytotoxic drugs into tumors by decreasing intratumoral pressure and normalizing dysfunctional vasculature and antiangiogenesis by direct action on endothelial cells (20–23). Whether these two proposed mechanisms play a substantial role in the eradication of micrometastasis is questionable (i.e., by definition, micrometastasis is characterized by the absence of supporting blood vessels and clearly does not show increased intratumoral pressure). Furthermore, whether the recently confirmed presence of VEGF receptors on tumor cells plays any role in early-stage colorectal cancer remains to be seen (24). Based on these considerations, it is conceivable that the addition of bevacizumab to conventional adjuvant chemotherapy might not lead to increased eradication of micrometastatic tumor cells, but could

| Table 1. Targeted agents currently tested in adjuvant colon cancer |
|---|---|---|
| **Anti-EGFR agents** | **Anti-VEGF agent** |
| Cetuximab | Panitumumab | Bevacizumab |
| Single-agent activity (RR) | ++ | ++ | (+) |
| Increased RR with chemotherapy | ++ | ? | + |
| Long-term safety | ? | ? | ? |
| Phase III trials in adjuvant colon cancer | Intergroup/NCTG N0147 and PETACC-8 | Not planned at present time | NSABP C-08 AVANT ECOG 5202 |

Abbreviations: ECOG, Eastern Cooperative Oncology Group; NCTG, North Central Cancer Treatment Group; NSABP, National Surgical Adjuvant Breast and Bowel Project; PETACC, Pan European Trial in Adjuvant Colon Cancer; RR, response rate.
prevent the formation of macrometastasis as long as bevacizumab is continued. In this case, an effect on DFS, but not long-term OS, might be observed in clinical trials. If, however, protracted VEGF deprivation by bevacizumab eventually leads to tumor cell apoptosis, a clinical benefit in OS might be observed with the use of adjuvant bevacizumab. In preclinical (and clinical) models, bevacizumab and other VEGF inhibitors have consistently been shown to reduce the number of tumor microvessels. Recent studies, however, have shown the rapid regrowth of blood vessels after withdrawal of inhibitors of VEGF signaling, with the suggestion that empty sleeves of basement and accompanying pericytes can provide a scaffold for the revascularization of tumors (25–27). In most current adjuvant clinical trials, these observations have prompted the continuation of bevacizumab for a prolonged period (i.e., an additional 6 months) after the discontinuation of conventional chemotherapy. Of note, bevacizumab is currently being evaluated in three large phase III adjuvant trials in colon cancer (National Surgical Adjuvant Breast and Bowel Project C-08, Eastern Cooperative Oncology Group 5202, and AVANT) and one phase III adjuvant trial in rectal cancer (Eastern Cooperative Oncology Group 5204).

### Cetuximab and Panitumumab

Two EGFR antibodies, cetuximab and panitumumab, have been approved by the Food and Drug Administration. Both have similar single-agent activity, and cetuximab has been shown to significantly increase the response rate of irinotecan- and oxaliplatin-based chemotherapy in the palliative setting (7, 28). Because both antibodies target a tumor cell-bound antigen (i.e., EGFR), their cytotoxic capabilities are conceivably more similar to those exhibited by conventional chemotherapy than bevacizumab. Such activity could result in the actual eradication of micrometastatic disease, with all caveats outlined above for the use of increased response as a marker for the efficacy of adjuvant therapy in the advanced disease setting. Unfortunately, few colorectal cancer tumors show relevant shrinkage with EGFR antibody therapy; response rates are in the range of 10% with single-agent therapy and 20% when used in combination with chemotherapy in the salvage therapy setting. Most recently, two phase III trials have been presented, which evaluated the efficacy of the addition of EGFR antibodies to standard first-line therapy (29, 30). The CRYSTAL trial (Cetuximab combined with irinotecan in first-line therapy for metaStatic colorectal cancer) compared FOLFIRI with FOLFIRI plus cetuximab as first-line therapy of metastatic colorectal cancer (30). Whereas the study end points were met, the incremental gain in progression-free survival of 0.9 months and the increase of response rate by 8.2% with the addition of cetuximab were clearly lower than expected. In addition, the Panitumumab Advanced Colorectal Cancer Evaluation trial did not show any improvement in response rate when panitumumab was added to FOLFOX plus bevacizumab (29). In fact, higher toxicity and a detrimental effect on progression-free survival and OS were found. Both trials underscore that EGFR antibodies have limited activity in unselected patients with colorectal cancer and that the definition of predictive factors to potentially enrich the patient population benefiting from these targeted agents is pertinent. No reliable predictor of EGFR antibody efficacy has yet been identified. In contrast to the HER-2 experience in breast cancer, EGFR expression assessed by immunohistochemistry has not been correlated with response to therapy (31). Thus, for all clinical trials in which EGFR antibodies are used as a component of adjuvant therapy, the patient population cannot be enriched to yield a higher chance of activity (and eventually superiority) in the experimental arm. Two phase III clinical trials [Intergroup/North Central Cancer Treatment Group NO147 and Pan European Trial in Adjuvant Colon Cancer 8] are currently under way to investigate cetuximab in combination with FOLFOX (i.e., oxaliplatin, leucovorin, and 5-FU) as adjuvant therapy in early-stage colon cancer.

### Is Disease-Free Survival Still a Valid Surrogate Marker of Overall Survival When Targeted Agents Are Used as Adjuvant Therapy?

A large meta-analysis established 3-year DFS as a valid surrogate marker for 5-year OS, the old gold standard of adjuvant therapy in colon cancer (3). The statistical model of this analysis postulates that the antituumor effect achieved with the administration of cytotoxic agents over a relatively short period of time (routinely 6 months) will translate into a treatment benefit sustained for 3 to 5 years. Although this concept might be true for the use of conventional chemotherapy (as it is in fact based on the assumption that micrometastatic disease is eliminated), it might not hold for biological targeted agents applied in the adjuvant setting. Figure 1 illustrates potential clinical scenarios that might contradict the universal acceptance of 3-year DFS as the preferred end point in adjuvant trials in colon cancer.

If the experimental arm of an adjuvant trial truly leads to the eradication of micrometastasis, the benefit observed at 3 years in terms of DFS will at least be sustained at the same magnitude at 5 years (Fig. 1, curve a). In fact, it is likely that the margin of benefit will actually widen over time. This scenario has been observed with the use of FOLFOX versus 5-FU/leucovorin in the MOSAIC trial. Interestingly, for MOSAIC, the recently presented 6-year OS data were found to show significant OS benefit for patients with stage III disease, thereby implying that the 5-year OS data did not reach statistical significance (10).
It is conceivable, however, that cytostatic biological agents will delay the manifestation of macrometastasis rather than eliminate occult tumor cells. Such an effect could result in a DFS curve showing a significant difference between the experimental and control arms at 3 years; however, the survival curves could subsequently converge so that no difference is noted at 5 years (Fig. 1, curve b).

In the worst case scenario, a biological agent might initially inhibit the manifestation of macrometastasis, but eventually exhibit tumor-promoting effects that could be detrimental to the long-term outcome of patients treated in the experimental arm (Fig. 1, curve c). This potential Janus-like effect of targeted agents has recently been highlighted in preclinical animal studies on Akt inhibitors that prevented local tumor growth but at the same time promoted invasion and metastasis in certain settings (32, 33). Thus, long-term follow-up beyond the current standard 5-year range might be required to definitively assess the effect of adjuvant therapy on OS.

Conclusions

Discussions of the caveats about the potential role of bevacizumab and EGFR antibodies in the adjuvant setting can be extrapolated to the growing number of targeted biological agents that will surely make their way into the treatment of colorectal cancer. Although preclinical models and hypotheses of the mechanism of action of these novel agents might suggest intriguing activity in early-stage disease, the rigorous tests of prospective clinical trials will eventually need to be passed. A better definition of predictive markers for each individual agent will be instrumental in the future to enrich the patient population that will benefit from their use in the potentially curative setting of early-stage disease. The potential risks involved as well as the financial burden associated with the use of targeted agents should preclude their use in the adjuvant setting until the definitive results of ongoing phase III trials are available.

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Biological Therapy and Other Novel Therapies in Early-Stage Disease: Are They Appropriate?

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