

ADVANCES IN ONCOLOGY

Current Developments in the Management of Solid Tumor Malignancies

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Novel Targets for Systemic Therapy of Colorectal Cancer

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H&O What is the background of the current research into novel targets for systemic therapy of colorectal cancer?

SK For the treatment of colorectal cancer, the model developed over the years is one of combination therapy, as exemplified by the addition of cytotoxic agents to 5-fluorouracil regimens, and more recently by the combination of monoclonal antibodies with cytotoxic agents. In other tumor types, development of new agents has proceeded as monotherapy, and colorectal cancer provides successful examples of combination therapy as the initial demonstration of efficacy for novel agents in both first-line and later settings. Beyond the use of combination therapy, there has been a trend of increased investigation of biomarkers earlier in the development of agents. I believe these trends will influence the next several years of trials.

H&O What are the most intriguing novel targets in colorectal cancer?

SK There are several broad classes of agents being developed for colorectal cancer, including antibodies against insulin-like growth factor (IGF), *Src* inhibitors, tumor necrosis factor–related apoptosis-inducing ligand (TRAIL) agonists, and mammalian target of rapamycin (mTOR) inhibitors. There also remains continued interest in finding new ways of targeting the angiogenic pathway besides the monoclonal antibodies, such as with pan–vascular endothelial growth factor receptor (VEGFR) tyrosine kinase inhibitors that are now under development.

Protein kinase C as a target is also under investigation in patients with metastatic colorectal cancer. There are other interesting targets at earlier stages of development, including poly(ADP-Ribose) polymerase (PARP) inhibitors, and cyclin-dependent kinase inhibitors.

IGF receptors are overexpressed in many colorectal cancers and have been correlated with outcome in many studies. This pathway has been associated with preclinical activity in colorectal cancer, and it is now under clinical investigation in combination regimens. Likewise, *Src* is a pathway that is activated in many colorectal cancers. In more advanced colorectal cancers, activation of *Src* has been found to be associated with prognosis. Inhibitors of *Src* have been investigated as monotherapy and also in combination with traditional cytotoxic agents and antibodies against epidermal growth factor receptor (EGFR).

There is also interest in mTOR inhibitors, given the activation of Pi3 kinase in colorectal cancer. Additionally, in a subset of colorectal cancers a mutation exists in genes encoding a subunit of the Pi3 kinase. It is hypothesized that this mutation may predict sensitivity to mTOR inhibition. A trial is currently ongoing using an enrichment strategy for such patients with a Pi3K mutation, seeking a subset of patients more sensitive to therapy.

Additionally, the angiogenic pathway has clearly been shown to be relevant in colorectal cancer with the clinical benefit of bevacizumab (Avastin, Genentech). VEGF tyrosine kinase inhibitors have been hypothesized to offer additional benefits over monoclonal antibodies against the angiogenic pathway, but this hypothesis has yet to be demonstrated clinically. Protein kinase C is one of the kinases demonstrated in colorectal and other cancers to be associated with growth signaling, and one

Table 1. Selected Ongoing Trials of Systemic Therapies in the Treatment of Colorectal Cancer

ClinicalTrials.gov Identification Number	Agent	Official Title	Phase
NCT00437268	Enzastaurin	A Randomized Phase 2 Study of Irinotecan Plus Cetuximab With or Without Enzastaurin in Patients With Recurrent Colorectal Cancer	II
NCT00384176	AZD2171	A Randomised, Double-Blind, Multicentre Phase II/III Study to Compare the Efficacy of Cediranib (RECENTIN, AZD2171) in Combination With FOLFOX, to the Efficacy of Bevacizumab in Combination With FOLFOX in Patients With Previously Untreated Metastatic Colorectal Cancer	II/III
NCT00460603	Axitinib	A Randomized Phase 2 Study of the Anti-Angiogenesis Agent AG-013736 in Combinations With Chemotherapy and Bevacizumab in Patients With Metastatic Colorectal Cancer Preceded by a Phase 1 Portion	II
NCT00504153	Dasatinib	A Phase II Study of Dasatinib (NSC 732517) in Previously-Treated Patients With Metastatic Colorectal Cancer	II
NCT00497497	Apomab	A Phase Ib, Dose-Escalation Study of the Safety and Pharmacokinetics of Apomab in Combination With Cetuximab and Irinotecan Chemotherapy in Patients With Previously Treated Metastatic Colorectal Cancer	I
NCT00419159	Everolimus	A Single Arm, Multicenter Phase II Study of Everolimus in Patients With Metastatic Colorectal Adenocarcinoma Whose Cancer Has Progressed Despite Prior Therapy With an Anti-EGFR Antibody (if Appropriate), Bevacizumab, Fluoropyrimidine, Oxaliplatin, and Irinotecan-Based Regimens	II/III
NCT00390364		Phase II Study of Single Agent RAD001 in Patients With Colon Cancer and Activating Mutations in the PI3KCA Gene	II
NCT00522665		Phase I / Randomized Phase II Study of Second Line Therapy With Irinotecan and Cetuximab With or Without RAD001, an Oral mTOR Inhibitor for Patients With Metastatic Colorectal Cancer: Hoosier Oncology Group GI05-102	I/II
NCT00503685	IMC-A12	A Randomized Phase II Clinical Trial of IMC-A12, as a Single Agent, or in Combination With Cetuximab, in Patients With Metastatic Colorectal Cancer With Disease Progression on Prior Anti-EGFR Therapy	II

protein kinase C inhibitor is currently undergoing late-phase clinical trials.

H&O What are the challenges with these novel types of therapy?

SK These novel systemic therapies all show promise, but there are practical limitations. Many of these agents are under development, as I mentioned, in combination regimens. In traditional single-arm phase II studies, determining efficacy of combination regimens can be difficult. The development route for many of these agents involves randomized phase II trial designs to compare a combination including the novel agent to a standard combination. As a result, this approach requires greater numbers of patients than traditionally have been used in single-agent studies looking for preliminary signs of efficacy. There are

other challenges relating to the biomarkers under development by many pharmaceutical companies for these agents. As prospective incorporation of biomarkers in the development pathway is a fairly new paradigm, there are no good models for how to move toward approval for individualized therapies based on biomarkers of efficacy. There is a great deal of interest in addressing this challenge in order to move forward in a uniform fashion. Furthermore, one goal of the development of biomarkers must be the concurrent validation of a biomarker testing platform and preparation for practical use in the clinic, which can present another degree of complexity.

Another challenge of metastatic colorectal cancer is the need to focus resources into testing appropriate agents. Although there are approximately 20,000 patients enrolled on the approximately 100 clinical trials currently open for metastatic colorectal cancer (Table 1), very

few—estimated at 13% of trials—are investigating agents against novel targets such as those I outlined. Furthermore, enrichment is the optimal setting for trying to identify and understand sensitive subsets, but only approximately 3% of trials now active are using an enrichment strategy in colorectal cancer. It is important that researchers utilize resources to investigate appropriate agents and to develop and incorporate biomarkers earlier in the process of drug development. When feasible, we should also try to move toward using enrichment strategies to identify subsets uniquely susceptible to treatment.

H&O What is your overall view of the research into novel targets for systemic therapy of colorectal cancer?

SK As a community, we have made progress. The number of agents in the pipeline continues to grow. Also promising is the expressed desire of pharmaceutical companies to develop agents that target sensitive subsets of patients with colorectal cancer. Previously, the concept of enrichment trials was not widely embraced, but there has been a realization that this strategy is a viable path to regulatory approval of an agent. As an example, it has recently been demonstrated, through retrospective and

subset analyses, that a subset of patients without mutations of *K-ras* achieve the vast majority of benefit from anti-EGFR monoclonal antibodies. It has become clear that there are many benefits to identifying such subsets earlier in the development process. Furthermore, alongside changes in trial strategies, we are improving our understanding of the biology of colorectal cancer. Developments in basic science continue to lead us to identify the best targets and to combine agents appropriately in order to maximize efficacy.

Suggested Readings

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