Targeted Therapy for Advanced Colorectal Cancer: Current Status

Presenter: Jordan D. Berlin, Associate Professor of Medicine and Clinical Director, GI Oncology, Vanderbilt-Ingram Cancer Center, Nashville, Tennessee

After nearly 50 years of research, three agents are recommended for use as the platform in colorectal cancer: 5-fluorouracil (5-FU), irinotecan (Camptosar, Pfizer), and oxaliplatin (Eloxatin, Sanofi-Synthelabo). Survival has been correlated with exposure of the patient to all three agents.

Despite extending the median survival time for advanced colon cancer to more than 20 months, however, it is not clear whether chemotherapy will be able to advance survival time even further. Longer survival will depend on the development of newer therapies.

Drugs that have an impact on two new targets—vascular endothelial growth factor (VEGF) and epidermal growth factor receptor (EGF-R)—have demonstrated beneficial activity in advanced colon cancer. Angiogenesis, the process of new blood vessel formation, is essential to the growth of cancer. The VEGF family of proteins is a primary activator of angiogenesis and lymphangiogenesis. Therapies that target VEGF and EGF-R are designed to stop the growth of cancer cells at the genetic and protein level.

**Bevacizumab**

Bevacizumab (Avastin, Genentech) is a monoclonal antibody that inhibits the most common form of VEGF, namely VEGF-A. In clinical trials, when added to chemotherapy (irinotecan, 5-FU, and leucovorin calcium), bevacizumab improved response rates, progression-free survival, and overall survival in colorectal cancer, compared with chemotherapy alone.

As a second-line therapy, bevacizumab also increased response rates, progression-free survival, and overall survival, compared with chemotherapy (FOLFOX, consisting of oxaliplatin, 5-FU, and leucovorin) alone. The effect of changing bevacizumab from a first-line to a second-line therapy is unknown. Given the potential for side effects, bevacizumab should not be used outside of clinical trials.

EGF-R is the second target successfully studied in colorectal cancer. In this case, the data are not as robust, because there is no evidence that these agents influence the survival of colorectal cancer patients.

Methods of inhibiting EGF have included monoclonal antibodies to the ligand-binding domain and small-molecule tyrosine kinase inhibitors. To date, several monoclonal antibodies have demonstrated activity in colorectal cancer.

**Cetuximab**

Cetuximab (IMC-C225, Erbitux, Bristol-Myers Squibb, ImClone) is a monoclonal antibody specific for EGF-R. It has produced reasonable response rates when used as a single agent (11%) and when combined with irinotecan in irinotecan-refractory colorectal cancer patients (23%).

**Panitumumab**

Panitumumab (Ammgen/Abgenix), a fully human immunoglobulin-2 (IgG2) antibody, was compared with the best supportive care in a randomized trial. Progression-free survival was significantly improved in the panitumumab arm.
Novel Biologics for Colorectal Cancer

Presenter: Howard S. Hochster, Professor of Medicine and Clinical Pharmacology, New York University Cancer Institute, New York City, New York

5-Fluorouracil (5-FU), now in use for 50 years, has been the mainstay of chemotherapy in the treatment of colorectal cancer, resulting in a one-year survival time. When biologic agents such as irinotecan and oxaliplatin are combined with 5-FU, survival time increases to about two years; therefore, this regimen remains the platform for treatment. Survival depends on the ability of patients to receive all three drugs. With the increase in research in colorectal cancer, molecular targets of treatment have identified the current agents that affect the angiogenesis pathway for tumor growth:

• bevacizumab
• sorafenib (BAY 43-9006, Nexavar, Bayer/Onyx)
• sutinib (SU 11248, Sutent, Pfizer)

Agents that affect the growth factor pathway include:

• trastuzumab (Herceptin, Genentech).
• cetuximab (Erbitux).
• erlotinib (Tarceva, OSI/Genentech).
• gefitinib (Iressa, AstraZeneca).

In treating colorectal cancer, one must consider cellular targets as well as pathways. Inhibiting the receptors can inhibit the pathways. Cellular targets include:

• VEGF-R.
• EGF-R.
• insulin-like growth factor receptor (IGF-R).
• platelet-derived growth factor receptor (PDGF-R).
• interleukin-1 receptor (IL-1-R).
• cell-surface receptor tyrosine kinase (c-Met).
• Ron, a tyrosine kinase receptor.
• urokinase-type plasminogen activator receptor (uPAR).
• tumor necrosis factor–related apoptosis-inducing ligand (TRAIL).

Vascular Endothelial Growth Factor Receptor

A pathway of particular interest in colorectal cancer is VEGF-mediated angiogenesis. In preclinical studies, VEGF has been the predominant angiogenic factor in human colorectal cancer. High levels of VEGF expression are associated with the development of metastases and a poor prognosis.

VEGF stimulates the growth of blood vessels in tumor cells. The use of monoclonal antibodies that bind to the external receptor and neutralize VEGF is one approach to anti-angiogenic therapy in colorectal cancer.

As of late 2006, the following pathways represented novel molecular targets:

• the angiogenesis pathway: VEGF-R-TKIs (an avian tyrosine kinase gene), VEGF-Trap (AVE 005)
• IGF-1R MoAb (monoclonal antibody)
• Src-TKIs

For the colorectal cancer cell, many targets include EGF-R, IGF-R, c-MET, VEGF-R1, uPAR, and integrins. Inhibiting any one of these targets influences other pathways. The best targeted therapies may be those that mediate cell survival.

Small-molecule inhibitors in clinical development include these first-generation agents:

• PTK 787/ZK 222584 (valatanib, Novartis)
• SU 5416 (semaxanib, Pharmacia)
• SU 6668
• SU 11248 (sunitinib).

Some new inhibitors are:

• AAL 993 (Novartis).
• CEP-7055 (Sanofi-Aventis).
• CP-547,632 (OSI).
• GW 654652 (GlaxoSmithKline).
• AMG 706 (Amgen).
• AZD 2171 (AstraZeneca).

Some combined inhibitors of VEGF, tyrosine kinase, and others include:

• ZD 6474 (Zactima, AstraZeneca).
• AEE 788 (Novartis).
• BAY 43-9006 (sorafenib).

Sorafenib inhibits RAF kinase and acts as an anti-VEGF molecule, producing stable disease without tumor shrinkage. AZD 2171 inhibits VEGF signaling. There is initial evidence of anti-tumor activity with good tolerability and a decrease in blood flow along with tumor shrinkage. VEGF Trap (AVE 0005) is a novel potent VEGF inhibitor protein that targets the VEGF pathway. Trap fusion proteins are soluble receptors that are created by fusing the extracellular domain of a growth factor or cytokine receptor to the Fc portion of immunoglobulin (IgG1). They are engineered to deliver high ligand affinity and extended half life in vivo.

VEGF Trap has high binding affinity for VEGF. It blocks VEGF-A and VEGF-B isoforms and placental growth factor. It is smaller than a monoclonal antibody and its elimination half-life is about two weeks in humans.

VEGF Trap is well tolerated at doses up to 5 mg/kg, and it has shown beneficial activity as a single agent in early clinical trials. Development is progressing rapidly.

Insulin Growth Factor Receptor Inhibitors

IGF-R-1 binds to either the IGF-I or the IGF-II receptor. IGF-I-R inhibitors in development include:

• monoclonal antibodies (human or humanized).
• NIMC-A12 (Imclone).
• CP-751,871 (Pfizer).
• AVE 1642 (Immunogen/Sanofi-Aventis).
• 19D2 (Schering-Plough).
Meeting Highlights: Chemotherapy Foundation Symposium, Part 2

Tyrosine Kinase Inhibitors
All tyrosine kinase inhibitors have the potential to inhibit insulin receptors. Tyrosine kinase inhibitors include:

- NVP-ADW 742 and NVP-AEW 541 (Novartis).
- BMS 536924 and BMS 554417 (Bristol-Myers Squibb).
- PPF (Karolinska Cancer Institute/Biovitrum).
- INS M 18 (Insmed).

The Src Oncogene
Src, an older oncogene, is a central mediator of growth factor receptor binding. Integrins that mediate through Src can stimulate cell survival through P1-3 K/Akt kinase system and other behavior of malignant cells. Src is also an active pathway of endothelial cell growth.

Src inhibitors exert a dual effect on tumor growth and endothelial cell growth. Src is a new target in colorectal cancer studies, because it is overexpressed in more than 80% of human colorectal cancer, resulting in a poor patient prognosis. Src activity increases with cancer progression. High concentrations of Src are more often found in metastases than in primary tumors. High expression is associated with epithelial-to-mesenchymal transitions (EMTs) and a poorer prognosis.

Src may be involved in EGF-R activation and escape from EGF-R inhibitors, and it disrupts sites at the periphery of cells involved in invasion and metastases.

Scr kinase inhibitors in development include:

- dasatinib (BMS-354825, Sprycel, Bristol-Myers Squibb).
- AP 23846 (Ariad).
- TG 100598 (TargetGen).
- AZD 0530 (AstraZeneca).
- SKI-606 (Wyeth).

Mammalian Target of Rapamycin
mTOR is another target for growth factor receptors through the PI3 kinase system. It comes downstream to mTOR receptor blocker. It is inhibited by RAD 001, an oral mTOR pathway receptor blocker.

RAD 001 (everolimus, Novartis) is an active rapamycin derivative; it is not a prodrug. Its half-life is 20 to 26 hours. It has cytotoxic CYP 3A4 metabolism and broad antitumor activity. It also inhibits cell growth, S-phase entry, and endothelial cells, and it enhances the action of molecular therapeutic agents that destroy the DNA of cancer cells. It is given on continuous daily and weekly schedules. In a phase 1 study, RAD 001 showed beneficial activity in patients with colon cancer. A phase 2 study of colorectal cancer is in progress.

Trends in Biologic Therapy
Combination chemotherapy is still the standard for treating colorectal cancer patients. A combination of three biologic drugs in patients has been effective in inhibiting angiogenesis and growth factors, leading to increased survival. The new targets in development include IGF-1, the Src oncogene, TRAIL, heat shock protein 90 (hsp-90), cyclin-dependent kinase (CDK), and mTOR. Future goals of drug development include improving survival, decreasing toxicity, identifying the correct target, and confirming adequate inhibition of the target.

RAV 12: A Monoclonal Antibody for Colon and Pancreatic Cancer

Presenter: Howard Burris III, MD, Director of Drug Development, Sarah Cannon Cancer Center, Nashville, Tennessee

RAV-12 (Raven Biotechnologies) is a high-affinity, internalizing, chimeric IgG1 monoclonal antibody that binds RAAG-12, a novel primate-restricted, N-linked carbohydrate epitope present on multiple cell-surface proteins. RAAG-12 is variably expressed on normal nonkeratinizing epithelia. It is not expressed on human tissues from the cardiovascular, endocrine, hematolymphatic, neuromuscular, or central nervous systems. In immunohistochemistry studies, more than 90% of human colon, gastric, and pancreatic adenocarcinoma samples bind RAV-12, indicating expression of RAAG-12.

A phase 1 study of RAV-12 is in progress to determine the agent’s maximum tolerated dose and pharmacokinetic profile. The study enrolled patients with metastatic or recurrent adenocarcinoma who had received one to three prior treatments. Patients with a disease other than colon, pancreatic, or gastric adenocarcinoma must have had a diagnosis of RAAG-12 expression as confirmed by archived or fresh tumor biopsies prior to treatment.

RAV-12 is administered weekly for four weeks, followed by repeated disease assessment on day 43. Patients with an objective partial or complete response may continue with RAV-12 therapy weekly until disease progression or unacceptable toxicity occurs.

Twenty-one patients have received treatment at three doses: 0.3 mg/kg (six patients), 1 mg/kg (eight patients), and 1.5 mg/kg (seven patients). Adverse reactions included abdominal cramping, pain, and diarrhea, particularly at the higher dose; asymptomatic, rapidly reversible abnormal levels of pancreatic enzymes; and elevated levels of lipase, alkaline phosphatase, and amylase.

One patient had grade 3 diarrhea. Three patients had stable disease as a best response at day 43. One patient, with pancreatic cancer, had a reduction of more than 50% in CA 19-9 (the pancreatic cancer antigen marker). The patient continued treatment for a total of nine doses, and disease stability was maintained for five months.

Another patient with metastatic colorectal cancer had a partial response to treatment (consisting of a 67% decrease in pulmonary disease and peritoneal adenopathy). This patient has continued to receive weekly antibody dosing for more than five months. Further experience is necessary with RAV-12 to evaluate its safety and efficacy.

Advances in Esophageal and Gastric Cancer

Presenter: David H. Ilson, MD, Associate Attending Physician and Associate Professor, Department of Medicine, GI Oncology Service, Well Medical College of Cornell University, Memorial Sloan-Kettering Cancer Center, New York, New York

Gastric Cancer
For locally advanced gastric cancer, two treatments, which are the standard of care for adjuvant therapy—postoperative
5-FU and radiation therapy—may improve survival better than surgery alone.

Recent data from the Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) study indicate that preoperative and postoperative therapy with the epirubicin/cisplatin/5-FU (ECF) regimen improved survival, compared with surgery alone, suggesting that preoperative therapy may play a role in the management of gastric cancer. Preoperative chemotherapy, however, did not improve the rate of curative resection, compared with surgery alone, and no pathological complete responses to chemotherapy were noted.

**Esophageal Cancer**

For esophageal cancer in the U.S., the use of concurrent radiation therapy, combined with preoperative chemotherapy (chemoradiotherapy) is the most common preoperative strategy. However, phase 3 trials using this approach have been small and underpowered, and they have shown only a trend toward improved survival, compared with surgery alone. Preoperative chemoradiotherapy improves rates of curative resection and leads to complete responses. In patients who are not surgical candidates, primary chemoradiotherapy represents an alternative local therapy option.

Cetuximab and bevacizumab, which target the EGF receptor and VEGF receptor ligand, respectively, are being evaluated in phase 2 clinical trials of preoperative chemoradiotherapy.

**Esophagogastric Cancer**

In patients with metastatic esophagogastric cancer, conventional chemotherapy employs continuous infusions of 5-FU in combination with cisplatin (Platino, Bristol-Myers Squibb). Response rates have ranged from 20% to 30%, yielding a median survival of only seven to eight months. When a third agent was added to cisplatin and 5-FU, including epirubicin (PharMor), docetaxel (Taxol, Bristol-Myers Squibb), response rates increased to 35% to 40%, and a one-month gain in median survival (nine months) was achieved, but at the cost of greater therapy-related toxicity.

Recent phase 3 trials have indicated that a non-cisplatin regimen, FUFIRI, may achieve antitumor efficacy and survival equivalent to that of 5-FU and cisplatin but with less toxicity. FUFIRI consists of 5-FU 425 mg/m² per day for five days and leucovorin 20 mg/m² per day for five days, followed by radiation treatment. In these trials, which are evaluating the substitution of either capcitabine (Xeloda, Roche) for 5-FU, or oxaliplatin for cisplatin (Eloxatin), activity has been comparable with the newer agents, with potentially less toxicity for oxaliplatin combination therapy.

In recent phase 1 and phase 2 trials, targeted agents that were added to chemotherapy include bevacizumab and matuzumab (EMD 72000, EMD Pharmaceuticals), which target the EGF receptor. Adding bevacizumab to weekly irinotecan (Camptosar) and cisplatin was possible in a recent phase 2 study and showed encouraging rates of response and time to tumor progression. These results indicate the need for a phase 3 evaluation of bevacizumab in esophagogastric cancer.

**Kinase-Targeted Drugs for Gastrointestinal Stromal Tumors**

**Presenter:** Robert Maki, Assistant Member, Department of Medicine, Melanoma/Sarcoma Program, Memorial Sloan Kettering Cancer Center, and Assistant Professor, Weill Medical College of Cornell University, New York, New York

GIST (the GI stromal tumor) is the most common type of soft-tissue sarcoma. Prior to the advent of therapy with imatinib mesylate (Gleevec, Novartis), surgery was the standard treatment. When tumors recurred after surgery, surgery was customarily repeated until it was no longer possible to keep operating. Before imatinib was available, standard chemotherapy was totally ineffective, and median survival was less than two years in patients with metastatic disease.

The standard of care for patients with GIST that is refractory to imatinib at 400 mg daily relies on increasing the dose of imatinib to as much as 800 mg daily. GIST patients with exon 11 c-kit mutations do better than those with exon 9 c-kit mutations or no c-kit mutations. Approximately 20% of subjects have continued receiving imatinib for more than five years, indicating that there is hope for long-term efficacy.

Because of the increasing frequency of imatinib resistance in GIST, phase 1/2 and phase 3 studies with the more potent c-kit inhibitor (an anti–VEGF-R agent) sunitinib (Sutent) were undertaken. The Food and Drug Administration (FDA) approved sunitinib in 2006 for imatinib-refractory GIST. Although a response rate of only 8% was observed in the phase 2 study, imatinib was associated with superior time to progression and overall survival in patients with metastases, compared with patients receiving placebo.

Agents that have not shown much efficacy in GIST include the mTOR inhibitor RAD 001 and the novel cytotoxic chemotherapy agent eceitnascidin (ET-743, PharMor).

Future studies will focus on the usefulness of multtargeted kinase inhibitors such as dasatinib (Sprycel), sorafenib ( Nexavar), AMG 706, and AMN 107 (nilotinib, Novartis) (along with imatinib). It must also be determined whether a continuous schedule of sunitinib would be superior to the FDA-approved schedule of four weeks on therapy, two weeks off.

Some newer agents have different mechanisms of action, including inhibitors of c-kit gene expression, for example, the heat shock protein-90 inhibitor IPI-504 (Infinity) and the cyclin-dependent kinase (CDK) inhibitor flavopiridol (Aventis, National Cancer Institute). These may represent the best options for combination therapies in the near future, because down-regulation of the pathway required for GIST cell survival may synergize with c-kit inhibition.

Surgery alone is thus the standard of care for primary GIST, and imatinib is the first-line therapy for metastatic disease. Sunitinib, approved for patients with GIST progressing on or intolerant to imatinib, also plays a role in treatment.