Managed Care Oncology

For Decision Makers in Managed Care
Quarter 1 2011

Diagnosis, Prognostic Factors, and Treatment Considerations for Colon Cancer

Current Initiatives and Future Directions
Balancing Survival Gains and Cost of Care
Managed Care Considerations
One goal: discovering and delivering breakthrough medicines to combat cancer.

Now the innovative science of a leading American biopharmaceutical company joins the global assets of Takeda, Japan’s largest pharmaceutical company, for a global commitment to oncology.

Millennium: The Takeda Oncology Company is developing an extensive pipeline — among the top in oncology worldwide — with more than 17 compounds in development for a broad range of solid and hematological cancers.

Our pipeline — rich in novel compounds — includes multiple candidates that target seven disease pathways: protein homeostasis, anti-angiogenesis, growth-signaling inhibition, cell-cycle inhibition, apoptosis, immunomodulators and hormone regulation.

We are dedicated to a strong partnership with the oncology community. Together we can make a dramatic impact on cancer therapeutics over the next decade.
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To learn more, visit us at millennium.com.
Improving Value
Managing Colon Cancer Care: Current Initiatives and Future Directions
by Matthew Mitchell, PharmD, MBA, Manager, Pharmacy Services, SelectHealth
Successful oncology therapy management is dependent upon the balanced consideration of both quality and cost components.

Drug Therapy Reviews
Managed Care Considerations in the Diagnosis, Staging, and Treatment of Colorectal Cancer
by Johanna Bendell, MD, Director, GI Oncology Research; Associate Director, Drug Development Unit, Sarah Cannon Research Institute
Colorectal cancer is one of the few cancers that has shown recent improvement in patient outcomes through enhanced screening efforts and advances in therapy.

Regulatory & Reimbursement
Colon Cancer: The Careful Balance of Survival Gains and Cost of Care
by Denise K. Pierce, President, DK Pierce & Associates, Inc.
Although colon cancer may not be managed care’s highest priority based on volume of patients, the cost of treating it on a per-patient basis can be significant, especially in later stages.

Industry Thought Leaders
A Discussion with Kevin Kobielski, CPA, Director, Pharmacy Services, HealthNow New York Inc.
ManagedCare Oncology recently sat down with Kevin Kobielski, CPA, Director, Pharmacy Services, HealthNow New York Inc., to gain insights on his plan’s integrated strategy for managing injectables.
The list of events that follows provides the dates and locations of upcoming meetings, workshops, and conferences of interest to managed care oncology professionals.

April
12-14 Pinsonault’s Managed Markets Summit
Miami, Florida
27-30 Academy of Managed Care Pharmacy’s 23rd Annual Meeting and Showcase
Minneapolis, Minnesota

May
10-13 7th Annual Armada Specialty Pharmacy Summit
Las Vegas, Nevada
17-19 Pinsonault’s Managed Care Account Management Training
Bonita Springs, Florida

June
3-7 American Society of Clinical Oncology’s 47th Annual Meeting
Chicago, Illinois
7-10 Canadian Orthopaedic Association’s 67th Annual Meeting
Ottawa, Ontario
15-17 America’s Health Insurance Plans’ Institute 2011
San Francisco, California

Dallas, Texas
29-30 22nd Annual Oncology Product Development Conference
San Antonio, Texas
4-7 American Academy of Ophthalmology’s Annual Meeting
San Francisco, California
18-20 American Society of Clinical Oncology’s 37th Annual Meeting
Chicago, Illinois
24-27 American Medical Association’s Annual Meeting
San Francisco, California
28-30 National Community Oncology Alliance’s National Symposium
San Diego, California

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Announcing a NEW J-Code for ARZERRA

- ARZERRA will have a permanent HCPCS code effective January 1, 2011
- The new J9302 Code replaces miscellaneous HCPCS Codes J9999, J3590, J3490, and C9260 that most providers have used to bill for ARZERRA to date

<table>
<thead>
<tr>
<th>HCPCS code</th>
<th>Description</th>
<th>Effective</th>
</tr>
</thead>
<tbody>
<tr>
<td>J9302</td>
<td>Injection, ofatumumab, 10mg</td>
<td>January 1, 2011</td>
</tr>
</tbody>
</table>

Contact your GSK representative for additional information or visit www.ARZERRA.com.
Since ManagedCare Oncology's founding in 2005, we have reviewed nearly all key cancers responsible for our country’s cancer-related morbidity and mortality. Because of its incidence and death rates – about 150,000 and 55,000 people annually – colorectal cancer (CRC) was reviewed in an early issue. In this issue, we are revisiting CRC, and Dr. Johanna Bendell of the Sarah Cannon Research Institute outlines current therapies and their efficacy.

I, on the other hand, want to tell you a quick story that will hopefully lead to earlier CRC screenings for you, your family, and your plan membership. By way of background, the current recommendations from the Centers for Disease Control and Prevention are that you should begin screening for CRC soon after turning age 50 and then continue getting screened at regular intervals. However, you may need to be tested earlier or more often than other people if:

- You or a close relative have had colorectal polyps or CRC
- You have inflammatory bowel disease
- You have a genetic syndrome such as familial adenomatous polyposis or hereditary nonpolyposis CRC

We studied the likelihood of payors having certain cancer-preventing programs in place (see Figure 1); colorectal cancer screening programs were reported as available to all members. However, as shown in

**Figure 1. Portion of Managed Care Lives Enrolled in Payors with Various Cancer Prevention Programs**

- Colonoscopy (CRC): 100%
- Mammography (BCA): 100%
- PSA testing (prostate CA): 77%
- Smoking prevention (NSCLC): 59%
Figure 2, on average, barely half of members older than age 50 actually get screened. Figure 3 indexes this for you by state (hint—think about your service area).

Okay, now on to the story. So this gentleman I know is a healthcare professional and has at least a working knowledge about cancer prevention and treatment. He was diagnosed with an allergy in his early 40s that required, shall we say, the same screening that one would use for CRC. Following the procedure, which apparently was much more benign than one is led to believe, he was told that the gastroenterologist removed five polyps and stated that “if the patient would have waited until the guideline recommendations (age 50) there would be a more than 50% chance he would be prescribing chemo.” Some time later, the gentleman remembered his father had a bowel resection a number of years ago and his sister had polyps removed as well. He then recalled that one-third of people younger than age 50 who are diagnosed with CRC have a family history. Talk about a shocker, total lack of self-awareness. By the way, you may have figured out who this gentleman is by now.

Please take another look at how you are screening for CRC at your plan; any improvements will save the lives of your members. Today, we pretty much understand why your members don’t get screened: the indignity of the procedure and/or financial issues, such as lost vacation days, copay burdens, and deductibles. I know you can mitigate the first issue and eliminate the other.

Kjel A. Johnson, PharmD
Publisher
ManagedCare Oncology

References
2. The 2010 EOCORE Healthcare Medical Injectables & Oncology Trend Report™
According to the American Cancer Society, colorectal cancer is the third most commonly diagnosed cancer and the third leading cause of cancer deaths among both men and women in the U.S. About 102,900 new cases of colon cancer and 39,670 new cases of rectal cancer were expected to occur in 2010. Incidence rates have been declining over the past two decades, which has been attributed to increased use of colorectal cancer screening tests.

Summary of Selected Risk Factors for Colorectal Cancer

<table>
<thead>
<tr>
<th>Factors That Increase Risk</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family history</td>
<td></td>
</tr>
<tr>
<td>One first-degree relative</td>
<td>2.2</td>
</tr>
<tr>
<td>More than one first-degree relative</td>
<td>4.0</td>
</tr>
<tr>
<td>Relative with diagnosis before age 45</td>
<td>3.9</td>
</tr>
<tr>
<td>Inflammatory bowel disease</td>
<td></td>
</tr>
<tr>
<td>Crohn’s disease colon</td>
<td>2.6</td>
</tr>
<tr>
<td>Ulcerative colitis colon</td>
<td>2.8</td>
</tr>
<tr>
<td>Ulcerative colitis rectum</td>
<td>1.9</td>
</tr>
<tr>
<td>Obesity (per five-unit increase in BMI)†</td>
<td></td>
</tr>
<tr>
<td>Men colon</td>
<td>1.3</td>
</tr>
<tr>
<td>Men rectum</td>
<td>1.1</td>
</tr>
<tr>
<td>Women colon</td>
<td>1.1</td>
</tr>
<tr>
<td>Alcohol consumption</td>
<td>1.1</td>
</tr>
<tr>
<td>Red meat consumption</td>
<td>1.3</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.3</td>
</tr>
<tr>
<td>Processed meat consumption</td>
<td>1.2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Factors That Decrease Risk</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Milk consumption (&lt; 70 vs. &gt; 250 g/day)</td>
<td>0.9</td>
</tr>
<tr>
<td>Calcium (includes supplements)</td>
<td>0.8</td>
</tr>
<tr>
<td>Physical activity (colon)</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>0.8</td>
</tr>
<tr>
<td>Women</td>
<td>0.7</td>
</tr>
</tbody>
</table>

† BMI = body mass index, calculated as weight in kilograms divided by height in meters squared.

* Relative risk compares the risk of disease among people with a particular exposure to the risk among people without that exposure. If the relative risk is more than 1.0, then risk is higher among exposed than unexposed persons. Relative risks of less than 1.0 reflect an inverse association between a risk factor and a disease, or a protective effect.
Stakeholder Insights

An ICORE Healthcare survey of health plan medical and pharmacy executives in 2009 found that the majority of health plans (57%) review coverage for therapies on an individual drug-by-drug basis when assessing metastatic colorectal cancer (mCRC) therapy options. The remainder, two out of five health plans, review coverage for therapies based on drug regimens, such as FOLFOX and FOLFIRI, which are prevalent mCRC treatment options.3

We wondered if payors look at managing mCRC through establishing a “preference” based on whether treatment is for the initial course of therapy postmetastatic diagnosis or whether it is for a course of therapy after disease progression. Most payors (70%) reportedly do not have a coverage preference for either therapy regimen, though one in five (21%) reported a preference for a FOLFOX-only regimen for the initial metastatic treatment. When asked the same question related to a preference after first progression of the metastatic disease, three-fourths expressed no preference, though of those who had a preference, one in 10 noted FOLFIRI. Following second progression, a few more payors noted a preference for the combination of FOLFOX/FOLFIRI.

Health Plan Preference Management for mCRC Regimens

<table>
<thead>
<tr>
<th></th>
<th>Initial mCRC Therapy</th>
<th>mCRC Therapy After First Progression</th>
<th>mCRC Therapy After Second Progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>FOLFOX only</td>
<td>21%</td>
<td>4%</td>
<td>2%</td>
</tr>
<tr>
<td>FOLFIRI only</td>
<td>0%</td>
<td>11%</td>
<td>2%</td>
</tr>
<tr>
<td>Combination of FOLFOX/FOLFIRI</td>
<td>9%</td>
<td>9%</td>
<td>15%</td>
</tr>
<tr>
<td>No preference for coverage</td>
<td>70%</td>
<td>75%</td>
<td>81%</td>
</tr>
</tbody>
</table>

In this same survey conducted by ICORE Healthcare, only about one-quarter of the health plan executives responded that they require every newly diagnosed mCRC patient to have a KRAS test performed to determine the KRAS status of the tumor prior to therapy initiation. This figure more than doubled in one year to 57% of payors.3 Additionally, payors reported wide variability in that many different KRAS tests are available in the marketplace. The College of American Pathologists notes that KRAS mutations can be detected in approximately 30% to 40% of all patients with CRC and highlights the importance of pathologist expertise in providing quality KRAS testing to enable physicians to make an effective patient treatment determination.4
Claims Benchmarks

This year, ICORE Healthcare analyzed a large claims data set from about 15 commercial payors to take a snapshot of the many common therapy regimens providers use to treat patients with colorectal cancers that are reimbursed by health plans. A 12-cycle cetuximab single-agent regimen is the most costly for a payor, regardless of the type of members who are insured or what methodology the payor utilizes.

The cetuximab/irinotecan combination regimen and panitumumab treatment are also high-cost therapies across health plan populations, making KRAS testing prior to treatment with these antiepidermal growth factor receptor monoclonal antibody agents a sound plan of action that will benefit the patient, the provider, and the health plan. How does your plan compare?

Colorectal Cancer Total Treatment Regimen Costs* by Type of Plan

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>irinotecan/leucovorin/5-fluorouracil/cetuximab</td>
<td>$24,179.25</td>
<td>$25,878.12</td>
<td>$61,023.95</td>
<td>$24,486.08</td>
<td>Every 14 days for 12 cycles</td>
</tr>
<tr>
<td>irinotecan/leucovorin/5-fluorouracil</td>
<td>$25,530.57</td>
<td>$27,229.44</td>
<td>$62,375.27</td>
<td>$24,486.08</td>
<td>Every 14 days for 12 cycles</td>
</tr>
<tr>
<td>XELOX</td>
<td>$64,905.71</td>
<td>$70,093.54</td>
<td>$86,640.41</td>
<td>$30,850.06</td>
<td>Every 21 days for eight cycles</td>
</tr>
<tr>
<td>panitumumab</td>
<td>$79,035.45</td>
<td>$85,548.15</td>
<td>$88,690.37</td>
<td>$75,483.41</td>
<td>Every 14 days for 12 cycles</td>
</tr>
<tr>
<td>mitomycin/5-fluorouracil</td>
<td>$29,664.37</td>
<td>$31,960.78</td>
<td>$43,451.28</td>
<td>$29,284.27</td>
<td>Every 21 days for eight cycles</td>
</tr>
<tr>
<td>irinotecan</td>
<td>$16,056.54</td>
<td>$17,260.26</td>
<td>$53,803.33</td>
<td>$17,984.40</td>
<td>Every 21 days for eight cycles</td>
</tr>
<tr>
<td>FLOX</td>
<td>$15,327.15</td>
<td>$16,495.17</td>
<td>$21,318.52</td>
<td>$15,137.98</td>
<td>Every 56 days for three cycles</td>
</tr>
<tr>
<td>cetuximab/irinotecan</td>
<td>$116,637.82</td>
<td>$126,452.64</td>
<td>$119,604.60</td>
<td>$111,910.14</td>
<td>Every 42 days for four cycles</td>
</tr>
<tr>
<td>capeRI</td>
<td>$41,946.33</td>
<td>$45,236.39</td>
<td>$57,280.20</td>
<td>$14,186.37</td>
<td>Every 21 days for eight cycles</td>
</tr>
<tr>
<td>capecitabine</td>
<td>$55,457.00</td>
<td>$59,842.99</td>
<td>$77,810.83</td>
<td>$17,984.40</td>
<td>Every 21 days for eight cycles</td>
</tr>
<tr>
<td>5-fluorouracil/leucovorin/oxaliplatin/bevacizumab</td>
<td>$14,941.22</td>
<td>$16,105.16</td>
<td>$20,896.54</td>
<td>$15,088.33</td>
<td>Every 56 days for three cycles</td>
</tr>
<tr>
<td>5-fluorouracil/leucovorin/oxaliplatin</td>
<td>$14,989.32</td>
<td>$16,157.34</td>
<td>$20,980.69</td>
<td>$15,137.98</td>
<td>Every 56 days for three cycles</td>
</tr>
<tr>
<td>irinotecan</td>
<td>$11,537.23</td>
<td>$12,424.12</td>
<td>$39,790.35</td>
<td>$15,273.19</td>
<td>Every 42 days for four cycles</td>
</tr>
<tr>
<td>cetuximab</td>
<td>$126,816.41</td>
<td>$137,249.67</td>
<td>$138,735.28</td>
<td>$119,955.58</td>
<td>Every 14 days for 12 cycles</td>
</tr>
<tr>
<td>5-fluorouracil</td>
<td>$11,424.13</td>
<td>$12,266.84</td>
<td>$18,634.53</td>
<td>$11,299.52</td>
<td>Every 28 days for six cycles</td>
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<tr>
<td>mFOLFOX</td>
<td>$103,184.39</td>
<td>$111,411.98</td>
<td>$119,740.00</td>
<td>$86,384.44</td>
<td>Every 14 days for 12 cycles</td>
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<tr>
<td>FOLFOX4</td>
<td>$101,833.07</td>
<td>$110,060.66</td>
<td>$118,388.68</td>
<td>$86,384.44</td>
<td>Every 14 days for 12 cycles</td>
</tr>
<tr>
<td>FOLFI</td>
<td>$25,530.57</td>
<td>$27,229.44</td>
<td>$62,375.27</td>
<td>$24,486.08</td>
<td>Every 14 days for 12 cycles</td>
</tr>
<tr>
<td>CapeOX</td>
<td>$49,832.58</td>
<td>$53,827.83</td>
<td>$66,323.91</td>
<td>$24,608.95</td>
<td>Every 28 days for six cycles</td>
</tr>
</tbody>
</table>

* Includes reimbursement for all drugs, support medications, and administrative codes for the entire duration of each regimen

References

3. ICORE Healthcare Payor Survey Research, 2009 (n = 53 payors, 123 million covered lives) and 2010 (n = 60 payors, 146 million covered lives).
5. ICORE Healthcare, paid medical claims for provider-administered drugs, 2006 to 2009, from approximately 15 commercial health plans.
Managing Colon Cancer Care: Current Initiatives and Future Directions

by Matthew Mitchell, PharmD, MBA, Manager, Pharmacy Services, SelectHealth
Successful oncology therapy management is dependent upon the balanced consideration of quality and cost components in tandem. This bilateral approach requires comprehensive deliberation of the unique challenges existing in each realm: clinical and financial.

Promoting evidence-based care among oncologists – including consistent use of pathways/guidelines among providers – and incorporating optimal medical treatment after exhausting first-, second-, and third-line therapeutic options are among the key oncology quality-of-care improvement challenges in managed care today. Critical oncology cost-of-care challenges facing managed care stakeholders include ensuring the appropriate use of oncologic medication therapies (i.e., identifying an appropriate treatment regimen that is tailored to an individual patient’s disease), defining the length of therapy, and assisting patients with cancer in achieving the best quality of life possible.

The management of colon cancer treatment, where clinical and financial considerations abound, is no exception to this approach. The National Comprehensive Cancer Network’s (NCCN) Clinical Practice Guidelines for colon cancer identify a number of different viable treatment options for each stage of the disease, and this complexity is compounded by the consideration of individual patient characteristics. On the financial side, colon cancer consistently ranks among the top three cancers in terms of national treatment expenditures and was second only to breast cancer in 2006, with an excess of $12 billion spent on care (see the figure on the next page). The emergence of targeted biologic therapies has contributed significantly to this trend, as more than 90% of the anticancer drugs approved during the last four years exceed $20,000 for a 12-week course of therapy. Considering the myriad of available therapeutic options, each characterized by varying efficacy and cost, the treatment of colon cancer is one area where health plans have focused significant attention in recent years.

THE SELECTHEALTH PERSPECTIVE
At SelectHealth, the pharmacy department’s oncology management program is anchored by ongoing utilization reviews of injectable and oral chemotherapies. This process is supplemented by ad hoc utilization reviews of specific drugs where diagnosis codes and specialty use are evaluated to determine if a particular medication may benefit from a prior authorization (PA) requirement. Condition- and provider-centric reporting further supports these efforts by providing network oncologists with a benchmark of where they stand with regard to prescribing appropriate therapy. In addition, the fee schedule is continually reviewed to ensure that the plan is not incentivizing cost-ineffective therapy or, perhaps even more importantly, de-incentivizing appropriate therapy.

In developing appropriate use or medical coverage policies, SelectHealth engages in ongoing communication with oncologists to ensure that the plan’s goals and providers’ goals are aligned in accordance with the plan’s specific coverage criteria. Several pipeline sources, conferences, and manufacturer communications are employed to obtain clinical information in identifying new indications for existing medications and new oncology drugs. The coverage of oncology therapies is largely based on U.S. Food and Drug...
Administration- (FDA-) approved indications; however, high-level DrugDex Compendia recommendations, specifically IIA or better, are also considered.

Although off-label use is a key cost driver in managed care, identifying all instances of this practice would be nearly impossible. Furthermore, the unfortunate reality is that – for some products and conditions – the standard of therapy may not be FDA-indicated, despite being clinically appropriate therapy. Still, SelectHealth has approximately 30 PAs in place to ensure the coverage of medication when sufficient supporting evidence exists. When we delve into this utilization management process further, drugs requiring PA must have the appropriate diagnosis code for approval. SelectHealth also uses another system to ensure an appropriate diagnosis code is used when a Healthcare Common Procedure Coding System (HCPCS) is billed. PAs are typically approved for six to 12 months, varying by drug, but the majority of oncologic therapies are approved for 12 months.

Looking toward the future, experts predict that up to 50% of the prospective oncology drug trend will likely be driven by new and existing specialty medications, especially monoclonal antibodies and small-molecule oral oncology drugs. With more than 800 new cancer therapies in the pipeline, plan costs for oncology drugs, especially the more targeted and long-term oral drugs, will continue to grow rapidly in the next three years. Due to the expense and rapid development of oral oncology therapies, SelectHealth manages oral drugs in a similar fashion as the injectable medications, particularly through PAs. In fact, some utilization management tactics are easier to employ for oral medications adjudicated through the pharmacy benefit, such as quantity limits.

CONSIDERATIONS IN THE MANAGEMENT OF COLON CANCER

One of the major challenges in the management of colon cancer from a plan standpoint is enhancing screening efforts to identify the disease in its initial stages, when it is easier and less costly to treat. On this front, SelectHealth reminds and incentivizes appropriate plan members for annual colon screening, which is also tracked as a Healthcare Effectiveness Data and Information Set (HEDIS) measure. In
terms of managing oncologic therapies specifically, the biologics remain the key cost drivers and require the highest level of oversight. For managing utilization of these therapies—namely, bevacizumab, cetuximab, and panitumumab—SelectHealth has PAs in place specific to the drugs’ FDA-labeled indications. In addition, plan stakeholders are constantly seeking opportunities to help select the ideal candidates for treatment with these costly biologics. Biomarkers are one such novel means of ensuring appropriate use of certain biologic therapies and are being put to use at SelectHealth for cetuximab and panitumumab, both of which require KRAS testing for PA. In addition to preventing inappropriate use in patients who will likely receive no benefit from certain costly treatments, these sophisticated tests also prevent undue adverse events from unnecessary therapy.

Beyond traditional utilization management initiatives, SelectHealth is rolling out a pilot project to monitor compliance with plan-preferred regimen use in the adjuvant treatment of colon cancer. Compliance with this measure is defined as use of one of three preferred treatment options postsurgery in stage II and stage III colon cancer patients. Beginning with one of the plan’s larger oncology clinics, results will be measured using retrospective claims analysis, and financial incentives will be provided to oncologists who demonstrate adequate compliance with the program. In addition to adjuvant treatment for colon cancer, supportive care will also be monitored in the pilot, specifically the use of antiemetics, colony-stimulating factors, and erythropoietin-stimulating agents.

One minor hurdle encountered prior to initiating the pilot was coming to an agreement on priorities and a starting point for the program. Adjuvant treatment was eventually selected due to the relatively limited number of available treatment options in this phase of therapy, and the resulting simplicity in getting a consensus decision from plan physicians on what regimens would be designated as preferred in the pilot. A larger barrier to implementation was determining how to accurately derive the compliance and noncompliance data from the claims. Because they come
in on HCPCS, there has been difficulty compiling claims on a line-by-line basis instead of by regimen. Similarly, in the supportive care pilot, patients must be receiving highly emetogenic chemotherapy for antiemetic therapy to be designated as compliant; as such, retrospective claims must be reviewed in order to make the determination.

CONCLUSIONS

Initiatives similar to SelectHealth’s adjuvant chemotherapy/supportive care pilot have been implemented by various managed care organizations across the country, taking on unique characteristics molded by each plan. This nationwide movement toward clinical pathways and guideline-based care demonstrates the collective recognition of excessive cost and suboptimal quality in managed care oncology. Traditional utilization management directives such as PA continue to play a vital role in overseeing the administration of oncology therapies, but the issue remains significant enough to warrant change. This especially holds true in the management of colon cancer, where the costs are high and the treatment options are many. Regardless of the approach, comprehensive consideration and design from plan stakeholders, coupled with cooperation and buy-in from network providers, remain crucial to improving quality of care and controlling costs.

References

Managed Care Considerations in the Diagnosis, Staging, and TREATMENT OF COLORECTAL CANCER

by Johanna Bendell, MD, Director, GI Oncology Research; Associate Director, Drug Development Unit, Sarah Cannon Research Institute

Colorectal cancer (CRC) is one of the few cancers that has shown recent improvement in patient outcomes, demonstrating declining incidence and mortality in the past two decades through enhanced screening efforts and advances in therapy.

Incidence rates have decreased from 66.3 cases per 100,000 persons in 1985 to 45.5 cases in 2006, and an accelerated decline has been observed from 1998 to 2006.1 Similarly, mortality rates for CRC have declined in the past two decades, with more significant reductions since 2001.1

Despite these notable improvements, 102,900 cases of colon cancer and 39,670 cases of rectal cancer were estimated to be diagnosed in 2010, representing between 9% and 10% of all new cancer cases.1 Specifically among adults ages 50 and younger, for whom screening is not recommended, CRC incidence rates have actually increased approximately 2% per year since 1994.1 Furthermore, CRC remains the second leading cause of cancer-related deaths in the United States, claiming an estimated 51,370 lives in 2010 (9% of all cancer-related deaths).1 The financial impact of CRC is likewise sizeable, resulting in upward of $12 billion in annual national expenditures.2 Taking into account this considerable burden, CRC continues to garner significant attention in managed care and warrants a closer look into the screening, diagnosis, and treatment of the disease.

RISK FACTORS AND SCREENING
In addition to the most prominent risk factor for CRC – advanced age, with 91% of cases being diagnosed in individuals ages 50 and older – several modifiable risk factors exist for the
disease. Among these modifiable risk factors are obesity, physical inactivity, heavy alcohol consumption, long-term smoking, and possibly a diet high in red or processed meat and/or inadequate intake of fruits and vegetables. Further highlighting the importance of diet in decreasing risk for this gastrointestinal cancer, consumption of milk and calcium appears to play a risk-reducing role as well. Specifically, individuals who have low levels of folate, vitamin D, and calcium tend to demonstrate higher risk for CRC. Beyond advanced age, other nonmodifiable risk factors for CRC include genetic predisposition (e.g., hereditary nonpolyposis colorectal cancer, or HNPCC), inflammatory bowel disease (e.g., Crohn’s disease, ulcerative colitis), diabetes, and acromegaly.

CRC is generally regarded as a cancer that can be detected in early stages due to effective screening methodology. While screening is not capable of entirely eradicating the incidence of CRC, a diagnosis of metastatic disease is undoubtedly less likely among regularly screened patients.

Individuals at increased or high risk for CRC should be screened before age 50 and/or be screened more frequently, as determined by their specific individual risk factor(s). Characteristics that qualify a patient as “high risk” include a personal and/or family history of CRC or adenomatous polyps, among others.

**DIAGNOSIS AND STAGING**

In the early stages of CRC, patients may be asymptomatic and require the aforementioned screening methods to detect the disease in this more treatable/curable state. These methods are also employed in symptomatic patients who present with anemia, fatigue, blood in the stool (as indicated by changes in color or consistency), and/or abdominal pain. A colonoscopy complete with biopsy is eventually employed in nearly all diagnoses, particularly in cases where it is indicated by the results of another means of screening (e.g., CT colonography, FOBT, FIT, sDNA) for confirmation of CRC.

After a colonoscopy and subsequent biopsy, patients generally undergo a CT scan of the abdomen/pelvis and chest (or chest X-ray), and a baseline carcinoembryonic antigen (CEA), a tumor marker, workup. In addition to their utility in diagnosing CRC, these tests also assist in staging the disease.

The clinical stage of a patient’s CRC can be determined by the results of the initial biopsy and imaging studies. Upon the patient undergoing surgery for the disease, which is eventually indicated in many cases, a patient’s pathologic stage may be ascertained from information not available through the less invasive previous tests; pathologic staging is required especially when there is no clinical evidence of distant disease. The American Joint Committee on Cancer’s (AJCC) staging system is the most commonly used method for staging CRC, featuring the standard number (0 through IV) and letter (A through C) designations based on tumor, node, and metastasis (i.e., TNM) criteria. As with other cancers,
this detailed staging system is a fairly reliable indicator of prognosis and five-year survival (see table).\(^6\)

These observed survival rates from Surveillance, Epidemiology, and End Results (SEER) studies underscore the importance of screening efforts to diagnose CRC in the initial stages, thereby improving the likelihood of treatment success.\(^6\) This proactive approach increases the odds that resection of the primary tumor via surgery will provide a complete cure, possibly with the addition of postoperative chemotherapy.

**PHARMACOTHERAPY**

Surgical resection offers the best opportunity for a complete cure in CRC; this strategy is augmented by the administration of pharmacotherapy, particularly chemotherapy and/or targeted biologics in the neoadjuvant and adjuvant settings. In addition to the pathologic stage of an individual patient’s disease, a wide array of other factors is considered when designing a treatment plan for CRC. Among these are the size and location of metastases, convertibility of the tumor(s), and risk factors that may preclude the patient from being a good candidate for surgery. The wishes of the patient and his or her comorbidities must also be considered when deciding upon a chemotherapy regimen, as the side effect profiles of certain agents are less attractive or potentially dangerous for patients with certain lifestyles or specific comorbid illnesses. For example, oxaliplatin is avoided in patients with lifestyles where fine dexterity is needed, such as musicians, as well as in patients with neuropathies at baseline. Performance status should be taken into account when determining treatment regimens as well. A pooled analysis by Goldberg et al. reported that patients with poor performance status (i.e., PS 2) derived similar advantages with regard to efficacy from aggressive therapy as PS 0-1 patients.\(^7\) However, for patients with decreased performance status secondary to significant comorbidities not likely associated with their cancers, many oncologists will avoid aggressive combination regimens that may have more significant toxicities. Another study of sequential chemotherapy treatments compared with combination regimens showed similar survivals with both approaches and less up-front toxicity with a sequential approach.\(^8\)

Patients with early-stage colon cancer and any number of confounding factors, such as lymph node involvement, poorly differentiated cancer, presentation with obstructive symptoms, and/or a perforated colon, should receive adjuvant chemotherapy post-surgery. Most often in these cases, a regimen of leucovorin, fluorouracil (5-FU), and oxaliplatin – collectively known as FOLFOX – is administered. In patients with stage II localized colon cancer and none of the previously mentioned risk factors, the use of adjuvant chemotherapy remains controversial, but 5-FU is commonly employed. Microsatellite instability, a marker of DNA mismatch repair (MMR) protein deficiency, appears to be a predictive indicator of nonresponse to chemotherapy and better overall outcomes that can be used to rule out adjuvant chemotherapy in stage II colon cancer patients in whom the treatment will offer no benefit.\(^9\)

Patients with metastatic colon cancer present an entirely different set of considerations. In some cases, the tumor (local tumor as well as metastatic disease) can be surgically resected without chemotherapy and still allow these patients a chance for cure. Sometimes neoadjuvant chemotherapy is employed to shrink the tumor and convert it from unresectable to resect-

---

**Observed Five-Year Survival Rates for Colon and Rectal Cancer**\(^4\)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Colon</th>
<th>Rectal</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>74%</td>
<td>74%</td>
</tr>
<tr>
<td>IIA</td>
<td>67%</td>
<td>65%</td>
</tr>
<tr>
<td>IIB</td>
<td>59%</td>
<td>52%</td>
</tr>
<tr>
<td>IIC</td>
<td>37%</td>
<td>32%</td>
</tr>
<tr>
<td>IIIA</td>
<td>73%</td>
<td>74%</td>
</tr>
<tr>
<td>IIIB</td>
<td>46%</td>
<td>45%</td>
</tr>
<tr>
<td>IIIC</td>
<td>28%</td>
<td>33%</td>
</tr>
<tr>
<td>IV</td>
<td>6%</td>
<td>6%</td>
</tr>
</tbody>
</table>
able. When the tumor is unresectable and cannot be converted, chemotherapy may be used to delay growth and progression, thereby holding the cancer at bay. The most common chemotherapy regimens used in the treatment of metastatic colon cancer include FOLFOX plus bevacizumab in the first line and FOLFIRI (leucovorin, 5-FU, and irinotecan) in the second line. The use of these initial regimens has remained relatively stable for the past five years as standards of care for patients with metastatic disease. Common third-line therapies for metastatic colon cancer include epidermal growth factor receptor (EGFR) inhibitors for patients with KRAS wild-type cancers as single agents or in combination with irinotecan. End-of-life care is generally indicated once the first three lines of therapy have been exhausted, although some clinicians will administer capecitabine or panitumumab as fourth-line treatment. Evaluation for clinical trials is available at research sites, academic or community, during all lines of therapy and for patients who are well enough to pursue treatment after receiving standard therapies.

Rectal cancer patients typically require chemotherapy and radiation therapy administered prior to surgery to control the tumor, thereby improving the chances of successful resection and prevention of local recurrence. One of the goals of therapy in these patients is to allow for sphincter-sparing surgery to prevent the need for a permanent colostomy bag. After surgery, patients with rectal cancer usually receive four months of adjuvant chemotherapy with FOLFOX.10

The effectiveness of neoadjuvant or adjuvant chemotherapy in the treatment of CRC varies depending on the patient’s individual disease characteristics. In general, localized or adjuvant therapy in stage III patients will decrease a patient’s odds of dying of the disease by 25%.11 For patients with advanced disease, there is approximately a 25% to 30% chance of cure if they are able to undergo potentially curative surgery.12 For those who undergo conversion therapy, conversion rates fit somewhere in this 30% range, but many of the available study results may be misrepresented by subjects with varying degrees of liver disease. In patients with metastatic disease that is not resectable, the average survival of patients with currently available therapy is approximately two years, which represents an improvement over an average survival of one year in the era where 5-FU was the only available therapy.

These recent improvements in survival are due to newer chemotherapies as well as biologic therapies such as bevacizumab, but the question remains as to whether there is a more cost-effective way to derive this extra survival. Feeling this relatively minimal survival benefit compared with standard chemotherapy was not enough to justify the cost of the biologic, the National Institute for Health and Clinical Excellence (NICE) recently issued a statement that the organization does not recommend the use of bevacizumab in the treatment of metastatic CRC.13 The United Kingdom’s health authority reviewed applicable data and cited an average additional six weeks of survival in patients receiving bevacizumab plus chemotherapy over patients receiving standard chemotherapy. Among the biologics, NICE recommends only cetuximab for the first-line treatment of metastatic CRC. Conversely, in the United States, the National Comprehensive Cancer Network (NCCN) recommends regimens including bevacizumab, cetuximab, and panitumumab in their treatment guidelines.
for metastatic CRC. This places the responsibility of managing utilization of these costly biologics solely on managed care organizations that must also have a number of other interventions in place to efficiently address the burden of CRC in a cost-effective manner.

FUTURE CONSIDERATIONS IN MANAGED CARE

In addition to traditional utilization management directives, managed care organizations are progressively employing evidence-based techniques to ensure the clinically appropriate and cost-effective administration of biologic therapies. The application of genomic techniques to determine gene expression in clinical samples of tumors from affected patients may further assist in the selection of particular treatment options, such as KRAS testing for EGFR inhibitors. Similarly, the identification of biologic markers may allow for additional classification of patients to aid in therapeutic selection, as is being practiced with microsatellite instability for stage II therapy. The prominence of these and similar interventions will likely increase in the future as additional advanced therapies enter the market, such as the new irinotecan-like agents; mitogen-activated protein kinase kinase (MEK), phosphatidylinositol 3-kinase (PI3K), and protein kinase A (Akt) inhibitors; and c-Met inhibitors.

Considering the improved survival and curability associated with CRC detected in its initial stages, enhanced screening efforts also demonstrate promise as a cost-effective approach to managing the disease. Accordingly, payors should work to improve screening rates within their plan populations via member incentives. Rather than actually paying patients for getting screened, these initiatives are often designed to remove financial disincentives by minimizing or eliminating member cost sharing for screening procedures. Although plans will undoubtedly incur up-front costs for these procedures upon eliminating cost sharing or offering discounts, payors will ultimately benefit from CRC treatment cost savings in the long run.

Despite the changing landscape of CRC therapy, the multidisciplinary approach remains crucial to the effective management of the disease. The central role of surgery in CRC treatment, coupled with the use of chemotherapy to improve outcomes, necessitates the involvement of both surgeons and medical oncologists (and radiation oncologists when applicable) in the care of patients. Input from all members of this collaborative team is particularly important in the initial diagnosis and treatment-planning processes; however, the importance of the multidisciplinary approach is maintained even in metastatic patients, for whom resection is the ultimate goal.

Beyond just collaboration among surgeons, medical oncologists, and radiation oncologists, plan stakeholders should strive to work with network physicians to ensure the clinically sound and cost-effective management of CRC. While oncologists must be ever mindful of treatment guidelines and appropriate use criteria, improved disease management cannot be achieved without concessions being made by the payor. Since the published literature and consensus recommendations often lag behind what has proven to be effective in the practice setting, some degree of trust must be placed in payors to make the best therapeutic decisions for their patients. Ideally, the medical review processes in place at managed care organizations will compensate for the hard-and-fast rules of guideline-based therapy authorization, but rising drug costs and limited payor resources are a real and present threat. Ultimately, practicing open communication and evidence-based medicine within plans will help to overcome these barriers and get payors and providers working toward the same goal: optimal patient care.

References
Colon cancer still remains the third leading cause of cancer death for men and women.

The National Cancer Institute (NCI) set estimates for colon cancer at 102,900 new cases and 51,370 deaths in the United States during 2010. However, there are glimmers of hope since new colon cancer cases are down almost 4% since 2006, and deaths from the disease are down 7% in that same time period. Most notably, colon cancer is the most preventable cancer and, with aggressive, consistent screening and early-stage intervention, can be cured.

Staging clearly plays a significant role in the colon cancer prognosis. Table 1 provides a statistical summary of NCI data on percentage of cases diagnosed by stage, with the corresponding five-year relative colon cancer survival rates.

Survival benefits have been obtained through the use of novel chemotherapy regimens and the entrance of targeted therapies that can provide a more predictable outcome for specific eligible patients. Although colon cancer may not be managed care’s highest priority based on volume of patients, the cost of treating colon cancer on a per-patient basis can be significant, especially in later stages of the disease.

Table 1. Stage and Survival

<table>
<thead>
<tr>
<th>Colon Cancer Stage</th>
<th>Percentage of Cases Diagnosed by Stage</th>
<th>Percentage Achieving Five-Year Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Localized (confined to the primary area)</td>
<td>39%</td>
<td>90%</td>
</tr>
<tr>
<td>Regional (spread to regional lymph nodes, or beyond the primary site)</td>
<td>37%</td>
<td>70%</td>
</tr>
<tr>
<td>Distant (metastasized)</td>
<td>19%</td>
<td>12%</td>
</tr>
<tr>
<td>Unknown/unstaged</td>
<td>5%</td>
<td>38%</td>
</tr>
</tbody>
</table>
In addition, cancer screening initiatives continue to diagnose patients earlier while they are still under commercial insurance. As a result, all payors (whether government or commercial) are taking a closer look at ensuring appropriate utilization for higher-cost chemotherapy, biologics, and targeted monoclonal antibodies.

**BIOMARKERS: PINPOINTING PATIENT SELECTION**

Acceptance of biomarkers as a means to establish patient selection has grown significantly in the medical community since 2009. For a managed care plan, the use of biomarkers has become a valuable way to help manage the concerns on inappropriate utilization of high-cost biologics.

The KRAS biomarker is one such example that is specific to colon cancer. Analyzing KRAS mutation within a colon tumor can determine response/nonresponse to targeted biologics. The drive toward payor coverage of the KRAS mutation occurred only after evidence of robust published trial data, coupled with parameters established by oncology guidelines and technology assessment organizations. Examples of reports, assessments, or published guidance that support utilization of the KRAS biomarker include those outlined in Table 2.

As of December 2010, research conducted with 35 managed care plans across the United States showed that 31 plans had formal published policies stipulating Erbitux (cetuximab) or Vectibix (panitumumab) coverage only for those patients who are KRAS-negative, using policy wording similar to the following:

"KRAS mutation analysis meets the definition of medical necessity to predict nonresponse to anti-EGFR monoclonal antibodies cetuximab and panitumumab in the treatment of metastatic colorectal cancer."  

In contrast, despite the fact that most late-stage colon cancer patients may be covered by Medicare benefits, only a select few Medicare contractors have specific local coverage determinations for oncology drugs and biologics, and even fewer contractors indicating KRAS mutation analysis requirements for the targeted therapies. Medicare contractors may change this coverage development position as they become more involved in evidence-based approaches for coverage decisions.

**Table 2. Support for Utilization of the KRAS Biomarker**

<table>
<thead>
<tr>
<th>Organization</th>
<th>Assessment/Report Title</th>
<th>Dates of Publication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blue Cross Blue Shield Technology Evaluation Center (BCBSTEC)</td>
<td>KRAS mutations and epidermal growth factor receptor inhibitor therapy in metastatic colorectal cancer</td>
<td>2008, 2009</td>
</tr>
<tr>
<td>American Society of Clinical Oncology (ASCO)</td>
<td>American Society of Clinical Oncology provisional clinical opinion: testing for KRAS gene mutations in patients with metastatic colorectal carcinoma to predict response to antiepidermal growth factor receptor monoclonal antibody therapy</td>
<td>2009</td>
</tr>
<tr>
<td>Agency for Healthcare Research and Quality (AHRQ)</td>
<td>Systematic reviews on selected pharmacogenetic tests for cancer treatments: CYP2D6 for tamoxifen in breast cancer, KRAS for anti-EGFR antibodies in colorectal cancer, and BCR-ABL1 for tyrosine kinase inhibitors in chronic myeloid leukemia</td>
<td>2010</td>
</tr>
</tbody>
</table>

**DRUGS AND BIOLOGICS: THE VALUE EQUATION**

The National Comprehensive Cancer Network’s (NCCN) Colon Cancer Guidelines commonly used as an important reference for assessment of clinical treatment decisions, outline several regimens to treat stage II and III, as well as advanced/metastatic colon cancer, including such treatments as:

- **FOLFOX**
- **FOLFIRI**
- 5-fluorouracil/leucovorin
- capecitabine +/- bevacizumab

* FOLFOX includes treatment with folinic acid (FOL), fluorouracil (F), and oxaliplatin (OX).
^ FOLFIRI includes treatment with folinic acid (FOL), fluorouracil (F), and irinotecan (IRI).

Payors recognize the potential for improving the quality of care and outcomes for patients with colon cancer, and the value of adding certain treatment options. However, there is a need to balance cost of care and benefit to patients, especially when considering the addition of high-cost targeted biologic therapies to current standard regimens that are relatively less costly.

The trend for managed care medical policies/medical management includes more specific criteria for utilization of higher-cost biologics, including such variables as:
1. International Classification of Diseases – Ninth Revision, Clinical Modification (ICD-9 CM) diagnosis code edits
2. Covered, acceptable drug combinations, based on clinical data (e.g., “use with a 5-fluorouracil-based chemotherapy treatment”)
3. Line of therapy limitations (e.g., “in patients refractory to irinotecan therapy”)
4. Specific dosing limits and frequency of dosing
5. Administration (utilization management) through specialty pharmacy mechanisms

FROM PATHWAYS TO PAYMENTS: THE NEXT STEPS
Based on 2010 research regarding payor integration of oncology cost management, an estimated 20% of payors were confirmed as currently using some form of clinical pathway. Approaches ranged from applying basic NCCN guidelines and treatment plan management to comprehensive target tumor/stage-of-disease pathways with payment assigned to compliance levels.11 By 2012, the estimate for incorporating such mechanisms as pathways is anticipated to grow to 40%. In all cases where pathways are currently in place, colon cancer is one of the top four primary tumor targets, based on cost of care.

In terms of payment evolution, United Healthcare’s current episode-of-care payment pilot model is perhaps the most transparent at this time, with a test of payments based on actual drug costs plus a case management fee. However, other payors and pathway organizations also are looking to potential episode-of-care models as a next step in utilization management. Medicare is also approaching episode-of-care payment across multiple care models (not necessarily oncology specific) by establishing a Medicare Shared Savings demonstration program for accountable care organizations (ACOs), which will encourage high-quality and efficient service delivery.12 Oncology practices are already positioning themselves to establish oncology medical homes or ACO models to take advantage of the Medicare Shared Savings approach.

EPILOGUE: TIPPING THE BALANCE TO THE POSITIVE
Colon cancer cost of care is a necessary focus for payors and providers as is the case for any higher-cost disease state. However, through the use of biomarkers and evidence-based medical policies, clinical pathways, and novel payment structures, management of utilization can be achieved without creating obstacles to patient access.

As a closing thought on balancing survival gains vs. cost of care, keep in your sights that colon cancer is the most preventable cancer. March is National Colon Cancer Awareness Month, offering a collaborative opportunity for payor and oncology provider communities to establish colon cancer prevention outreach.

References
In this era of personalized medicine and targeted therapies, colon cancer treatment continues to be centered around the appropriate use of the oxaliplatin- and irinotecan-based regimens while the development of new agents is explored.

The identification of molecular targets has yielded promising results in a variety of solid tumors, including lung cancer, breast cancer, and melanoma, but such advances are lacking in colon cancer.

Studies have shown that patients with KRAS mutated tumors do not benefit from the epidermal growth factor receptor (EGFR) inhibitors, although it is unclear if any of the newer biologics are active in this subgroup. Additional data from the NORDIC VII study reveals no benefit for the oxaliplatin combinations plus cetuximab. The strongest results from the EGFR monoclonal antibodies plus chemotherapy regimens are with irinotecan plus cetuximab, such as in the CRYSTAL and BOND trials.

There seems to be a story of synergy with the EGFR inhibitors and DNA-damaging agents such as the
topoisomerase inhibitors, particularly irinotecan. Cetuximab, at least preclinically, suppresses DNA repair and increases proapoptotic molecules, which render cells more sensitive to cytotoxic chemotherapy. Lastly, certain multidrug resistance gene (MDR1) polymorphisms decrease SN-38 (camptothecin) efflux in the setting of EGFR inhibition, which increases chemotherapy potency.

There is excitement around the c-Met and hepatocyte growth factor (HGF) pathway and its role in colon cancer. A number of these agents, both small molecules and monoclonal antibodies, have been designed against this target. Initial trial results from the AMG 102 (Amgen) HGF Ab plus panitumumab against previously treated KRAS wild-type colon cancer report a 31% objective response rate (ORR). The other arm of this small randomized study evaluated AMG 179 (Amgen), an insulin growth factor 1 receptor inhibitor (IGF-1R) Ab plus panitumumab, and a 21% ORR was noted. No increased or cumulative toxicities were noted with the addition of these biologics to the EGFR-I Ab.

The ARQ 197 (Arqule) small-molecule c-Met inhibitor has been studied in an early study in combination with irinotecan and cetuximab. Multiple signs of antitumor activity have been noted, including a complete response. Other c-Met inhibitors are in development by Incyte/Novartis and Genentech/Roche. The MetMAb inhibitor (Genentech/Roche) yielded outstanding results in c-Met overexpressing previously treated lung cancer patients when given in combination with erlotinib. These results, presented at the European Society for Medical Oncology meeting in October 2010 by David Spigel of the Sarah Cannon Research Institute, demonstrated improvements in both progression-free survival and overall survival with a hazard ratio of 0.55.

Approximately 10% of colon cancers have a BRAF mutation, and both BRAF and mitogen-activated protein kinase (MEK) inhibitors are being evaluated in this population. No clinical results have been reported to date, but there is clear enthusiasm for this strategy.

The ultimate promise with new agents is their impact in the adjuvant setting where it is hopeful more patients can be potentially cured. Unfortunately, we now have a second study (AVANT) with bevacizumab (Avastin/Genentech) that did not yield positive results. AVANT enrolled stage III patients receiving either FOLFOX (leucovorin, fluorouracil [5-FU], and oxaliplatin) or XELOX who were then randomized to bevacizumab or placebo. Similar to the NSABP C08 study, a benefit for bevacizumab was noted at the end of year one, but that advantage did not hold up in years two and three. The cetuximab adjuvant studies with oxaliplatin regimens have been negative, as have been prior irinotecan-based adjuvant regimens. That said, the N0147 study subset of FOLFIRI (leucovorin, 5-FU, and irinotecan)/cetuximab [40 patients] yielded encouraging results and suggested a larger study to assess the synergy mentioned above is warranted.

New targets, better biomarkers, and correlative studies within clinical trials are required if we are to take the next step in improving the care of colon cancer patients. Participation in a clinical trial is the first step in fighting cancer, not the last.
TREATMENT OF Colon Cancer

With each publication, ManagedCare Oncology’s Drug & Administration Compendia highlights a single medication or a group of medications that could be utilized in the management of one of the featured oncology diseases.

This section addresses such topics as:
- Associated ICD-9-CM codes
- Drugs that have been FDA-approved
- Drugs that are compendia-listed for off-label use based on clinical studies that suggest beneficial use in some cases
- Ancillary medications used in cancer treatment
- Reimbursement and coding information
  - HCPCS/CPT® codes and code description
  - Current code price (AWP-based pricing)
  - Most recent Medicare allowable (ASP + 6%), if applicable
  - Possible CPT® administration codes that can be utilized with each drug

Associated ICD-9-CM Codes:

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
</table>
| 153  | Malignant neoplasm of colon
|      | Excludes benign carcinoid tumor of colon (209.50-209.56)
|      | Malignant carcinoid tumor of colon (209.10-209.16)

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>153.0</td>
<td>Hepatic flexure</td>
</tr>
<tr>
<td>153.1</td>
<td>Transverse colon</td>
</tr>
<tr>
<td>153.2</td>
<td>Descending colon</td>
</tr>
<tr>
<td></td>
<td>Left colon</td>
</tr>
<tr>
<td>153.3</td>
<td>Sigmoid colon</td>
</tr>
<tr>
<td></td>
<td>Sigmoid (flexure) Excludes rectosigmoid function (154.0)</td>
</tr>
<tr>
<td>153.4</td>
<td>Cecum</td>
</tr>
<tr>
<td></td>
<td>Ileocecal valve</td>
</tr>
<tr>
<td>153.5</td>
<td>Appendix</td>
</tr>
<tr>
<td>153.6</td>
<td>Ascending colon</td>
</tr>
<tr>
<td></td>
<td>Right colon</td>
</tr>
<tr>
<td>153.7</td>
<td>Splenic flexure</td>
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<tr>
<td>153.8</td>
<td>Other specified sites of large intestine</td>
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<tr>
<td></td>
<td>Malignant neoplasm of contiguous or overlapping sites of colon with point of origin that cannot be determined Excludes ileocecal valve (153.4) rectosigmoid function (154.0)</td>
</tr>
<tr>
<td>153.9</td>
<td>Colon, unspecified</td>
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<td></td>
<td>Large intestine NOS</td>
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FDA-Approved Medications Currently Available to Treat Colon Cancer

<table>
<thead>
<tr>
<th>generic (Brand) Name</th>
<th>HCPCS Code – Code Description</th>
<th>Current Code Price (AWP-Based Pricing) Effective 1/1/11</th>
<th>Medicare Allowable (ASP + 6%) – Effective 1/1/11–3/31/11</th>
<th>CPT® Administration Code(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>bevacizumab (Avastin)</td>
<td>J9035 – injection, bevacizumab, 10 mg</td>
<td>$70.04</td>
<td>$59.67</td>
<td>96413, 96415</td>
</tr>
<tr>
<td>capecitabine (Xeloda)</td>
<td>J8520 – capecitabine, oral, 150 mg</td>
<td>$8.52</td>
<td>$6.91</td>
<td>N/A</td>
</tr>
<tr>
<td>capecitabine (Xeloda)</td>
<td>J8521 – capecitabine, oral, 500 mg</td>
<td>$28.41</td>
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<tr>
<td>cetuximab (Erbitux)</td>
<td>J9055 – injection, cetuximab, 10 mg</td>
<td>$58.46</td>
<td>$49.74</td>
<td>96413, 96415</td>
</tr>
<tr>
<td>fluorouracil (Adrucil)</td>
<td>J9190 – injection, fluorouracil, 500 mg</td>
<td>$3.37</td>
<td>$1.75</td>
<td>96409</td>
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<td>irinotecan (Camptosar)</td>
<td>J9206 – injection, irinotecan, 20 mg</td>
<td>$31.48</td>
<td>$7.64</td>
<td>96413, 96415</td>
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<tr>
<td>leucovorin calcium (Wellcovorin)</td>
<td>J0640 – injection, leucovorin calcium, per 50 mg</td>
<td>$3.60</td>
<td>$1.05</td>
<td>96372, 96374, 96409</td>
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<td>oxaliplatin (Eloxatin)</td>
<td>J9263 – injection, oxaliplatin, 0.5 mg</td>
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<td>$9.14</td>
<td>96413, 96415</td>
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<tr>
<td>panitumumab (Vectibix)</td>
<td>J9303 – injection, panitumumab, 10 mg</td>
<td>$101.85</td>
<td>$87.33</td>
<td>96413, 96415</td>
</tr>
</tbody>
</table>
## Compendia-Listed Off-Label Use Medications Currently Available to Treat Colon Cancer

<table>
<thead>
<tr>
<th>generic (Brand) Name</th>
<th>HCPCS Code – Code Description</th>
<th>Current Code Price (AWP-Based Pricing) Effective 1/1/11</th>
<th>Medicare Allowable (ASP + 6%) – Effective 1/1/11-3/31/11</th>
<th>CPT® Administration Code(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacillus Calmette-Guerin (Tice BCG, TheraCys)</td>
<td>J9031 – BCG (intravesical), per installation</td>
<td>$169.10</td>
<td>$113.60</td>
<td>51720</td>
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<tr>
<td>Carmustine (BiCNU)</td>
<td>J9050 – injection, carmustine, 100 mg</td>
<td>$205.69</td>
<td>$175.91</td>
<td>96413, 96415</td>
</tr>
<tr>
<td>Cisplatin (Platinol AQ)</td>
<td>J9060 – injection, cisplatin, powder or solution, per 10 mg</td>
<td>$4.33</td>
<td>$1.59</td>
<td>96409, 96413, 96415</td>
</tr>
<tr>
<td>Doxorubicin (Adriamycin)</td>
<td>J9000 – injection, doxorubicin hydrochloride, 10 mg</td>
<td>$13.20</td>
<td>$4.06</td>
<td>96409</td>
</tr>
<tr>
<td>Flouxuridine (HIDR)</td>
<td>J9200 – injection, flouxuridine, 500 mg</td>
<td>$121.06</td>
<td>$37.59</td>
<td>96422, 96423, 96425</td>
</tr>
<tr>
<td>Levoeleucovorin calcium (Fusilev)</td>
<td>J0641 – injection, levoeleucovorin calcium, 0.5 mg</td>
<td>$2.12</td>
<td>$1.26</td>
<td>96365, 96366</td>
</tr>
<tr>
<td>Lomustine (CeeNII)</td>
<td>J8999* – prescription drug, oral, chemotherapeutic, not otherwise specified</td>
<td>NDC level pricing</td>
<td>NDC level pricing</td>
<td>N/A</td>
</tr>
<tr>
<td>Lomustine (CeeNII)</td>
<td>S0178 – lomustine, oral, 10 mg</td>
<td>$10.59</td>
<td>S0178 – not payable by Medicare</td>
<td>N/A</td>
</tr>
<tr>
<td>Methotrexate sodium</td>
<td>J9250 – methotrexate sodium, 5 mg</td>
<td>$0.29</td>
<td>$0.20</td>
<td>96372, 96374, 96401, 96409, 96450</td>
</tr>
<tr>
<td>Methotrexate sodium</td>
<td>J9260 – methotrexate sodium, 50 mg</td>
<td>$2.86</td>
<td>$2.01</td>
<td>96372, 96374, 96401, 96409, 96450</td>
</tr>
<tr>
<td>Mitomycin (Mutamycin)</td>
<td>J9280 – mitomycin, 5 mg</td>
<td>$67.20</td>
<td>$21.73</td>
<td>96409</td>
</tr>
<tr>
<td>Mitoxantrone (Novantrone)</td>
<td>J9293 – injection, mitoxantrone hydrochloride, per 5 mg</td>
<td>$106.50</td>
<td>$41.22</td>
<td>96409, 96413</td>
</tr>
<tr>
<td>Pemetrexed (Alimta)</td>
<td>J9305 – injection, pemetrexed, 10 mg</td>
<td>$62.70</td>
<td>$52.34</td>
<td>96409</td>
</tr>
<tr>
<td>Streptozocin (Zanosar)</td>
<td>J9320 – injection, streptozocin, 1 g</td>
<td>$349.23</td>
<td>$274.58</td>
<td>96409, 96413, 96415</td>
</tr>
<tr>
<td>Teniposide (Vumon)</td>
<td>Q017 – injection, teniposide, 50 mg</td>
<td>$376.55</td>
<td>$322.77</td>
<td>96413, 96415</td>
</tr>
<tr>
<td>Topotecan (Hycamtin)</td>
<td>J8705 – topotecan, oral, 0.25 mg</td>
<td>$89.73</td>
<td>$77.12</td>
<td>N/A</td>
</tr>
<tr>
<td>Topotecan (Hycamit)</td>
<td>J9351 – injection, topotecan, 0.1 mg</td>
<td>$23.69</td>
<td>$27.35</td>
<td>96413</td>
</tr>
<tr>
<td>Vincristine (Vincasar PFS)</td>
<td>J9370 – vincristine sulfate, 1 mg</td>
<td>$5.83</td>
<td>$3.87</td>
<td>96409</td>
</tr>
</tbody>
</table>

*When billing a nonclassified medication using a CMS 1500 claim form, you must include both the HCPCS code (i.e., J8999 for CeeNII) in column 24D and the drug name, strength, and NDC (National Drug Code) in box 19 to ensure appropriate reimbursement.
Ancillary Medications Used in Cancer Treatment

<table>
<thead>
<tr>
<th>generic (Brand) Name</th>
<th>HCPCS Code – Code Description</th>
<th>Current Code Price (AWP-Based Pricing) Effective 1/1/11</th>
<th>Medicare Allowable (ASP + 6%) – Effective 1/1/11-3/31/11</th>
<th>CPT® Administration Code(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>aprepitant (Emend)</td>
<td>J8501 – aprepitant, oral, 5 mg</td>
<td>$7.12</td>
<td>$5.99</td>
<td>N/A</td>
</tr>
<tr>
<td>granisetron (Kytril)</td>
<td>J1626 – injection, granisetron hydrochloride, 100 mcg</td>
<td>$3.89</td>
<td>$0.65</td>
<td>96374</td>
</tr>
<tr>
<td>granisetron (Kytril)</td>
<td>Q0166 – granisetron hydrochloride, oral, 1 mg, FDA-approved prescription antiemetic, for use as a complete therapeutic substitute for an IV antiemetic at time of chemotherapy treatment, not to exceed a 24-hour dosage regimen</td>
<td>$59.01</td>
<td>$0.78</td>
<td>N/A</td>
</tr>
<tr>
<td>granisetron (Kytril)</td>
<td>S0091 – granisetron hydrochloride, 1 mg (For circumstances falling under the Medicare statute, use Q0166.)</td>
<td>$59.01</td>
<td>S0091 – not payable by Medicare</td>
<td>N/A</td>
</tr>
<tr>
<td>ondansetron (Zofran)</td>
<td>J2405 – injection, ondansetron hydrochloride, per 1 mg</td>
<td>$0.60</td>
<td>$0.17</td>
<td>96372, 96374</td>
</tr>
<tr>
<td>ondansetron (Zofran)</td>
<td>Q0179 – ondansetron hydrochloride, oral, 8 mg, FDA-approved prescription antiemetic, for use as a complete therapeutic substitute for an IV antiemetic at time of chemotherapy treatment, not to exceed a 48-hour dosage regimen (Code price is per 8 mg.)</td>
<td>$39.36</td>
<td>$1.08</td>
<td>N/A</td>
</tr>
<tr>
<td>ondansetron (Zofran)</td>
<td>S0181 – ondansetron hydrochloride, oral, 4 mg (For circumstances falling under the Medicare statute, use Q0179.)</td>
<td>$23.98</td>
<td>S0181 – not payable by Medicare</td>
<td>N/A</td>
</tr>
<tr>
<td>palonosetron (Aloxi)</td>
<td>J2469 – injection, palonosetron hydrochloride, 25 mcg</td>
<td>$43.20</td>
<td>$18.87</td>
<td>96374</td>
</tr>
</tbody>
</table>

CPT® Administration Code Descriptions

<table>
<thead>
<tr>
<th>CPT® Administration Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>51720</td>
<td>Bladder instillation of anticarcinogenic agent (including retention time)</td>
</tr>
<tr>
<td>96401</td>
<td>Chemotherapy administration, subcutaneous or intramuscular; nonhormonal antineoplastic</td>
</tr>
<tr>
<td>96402</td>
<td>Chemotherapy administration, subcutaneous or intramuscular; hormonal antineoplastic</td>
</tr>
<tr>
<td>96409</td>
<td>Chemotherapy administration, intravenous push technique, single or initial substance/drug</td>
</tr>
<tr>
<td>96413</td>
<td>Chemotherapy administration, intravenous infusion technique; up to one hour, single or initial substance/drug</td>
</tr>
<tr>
<td>96415</td>
<td>Chemotherapy administration, intravenous infusion technique; each additional hour (List separately in addition to code for primary procedure.) (Use 96415 in conjunction with 96413.)</td>
</tr>
<tr>
<td>96422</td>
<td>Chemotherapy administration, intra-arterial; infusion technique, up to one hour</td>
</tr>
<tr>
<td>96423</td>
<td>Chemotherapy administration, intra-arterial; infusion technique, each additional hour (List separately in addition to code for primary procedure ) (Use 96423 in conjunction with 96422.)</td>
</tr>
<tr>
<td>96425</td>
<td>Chemotherapy administration, intra-arterial; infusion technique, initiation of prolonged infusion (more than eight hours), requiring the use of a portable or implantable pump</td>
</tr>
<tr>
<td>96450</td>
<td>Chemotherapy administration, into CNS (e.g., intrathecal), requiring and including spinal puncture</td>
</tr>
<tr>
<td>96365</td>
<td>Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); initial, up to one hour</td>
</tr>
<tr>
<td>96366</td>
<td>Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); each additional hour (List separately in addition to code for primary procedure.) (Use 96366 in conjunction with 96365, 96367.)</td>
</tr>
<tr>
<td>96369</td>
<td>Subcutaneous infusion for therapy or prophylaxis (specify substance or drug); initial, up to one hour, including pump setup and establishment of subcutaneous infusion site(s)</td>
</tr>
<tr>
<td>96370</td>
<td>Subcutaneous infusion for therapy or prophylaxis (specify substance or drug); each additional hour (List separately in addition to code for primary procedure. ) (Use 96370 in conjunction with 96369.)</td>
</tr>
<tr>
<td>96372</td>
<td>Therapeutic, prophylactic, or diagnostic injection (specify substance or drug); subcutaneous or intramuscular</td>
</tr>
<tr>
<td>96374</td>
<td>Therapeutic, prophylactic, or diagnostic injection (specify substance or drug); intravenous push, single or initial substance/drug</td>
</tr>
</tbody>
</table>

References

- RJ Health Systems International, LLC. The Drug Reimbursement Coding and Pricing Guide. Volume 8, Number 1, First Quarter, 2011.
- FDA-approved indication (product-prescribing information).
- Compudex references available upon request.

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This information was supplied by RJ Health Systems International LLC, located in Wethersfield, Conn. Prices and information supplied herein are effective as of January 1, 2011.
### Oncology-Related HCPCS Codes

This reference chart will assist the Oncology Office (office manager, oncology nurse, physician, and ancillary staff) and payor with the appropriate codes to utilize when billing or reimbursing for medication(s).

<table>
<thead>
<tr>
<th>Generic (Brand) Name</th>
<th>HCPCS Code – Code Description</th>
<th>FDA-Approved Uses</th>
<th>Compendia-Listed Off-Label Uses</th>
<th>Current Code Price (AWP-Based Pricing)*</th>
<th>Medicare Allowable (ASP + 6%) **</th>
<th>CPT® Admin Code(s)</th>
</tr>
</thead>
</table>
| azacitidine (Vidaza)  | J9025 – injection, azacitidine, 1 mg | Myeloid leukemia – chronic (205.1_)
Low-grade myelodysplastic syndrome lesions (238.72)
High-grade myelodysplastic syndrome lesions (238.73)
Myelodysplastic syndrome with 5q deletion (238.74)
Myelodysplastic syndrome, unspecified (238.75) | Malignant neoplasm of retroperitoneum and peritoneum – specified parts of peritoneum (158.8)
Malignant neoplasm of retroperitoneum and peritoneum – unspecified (158.9)
Malignant neoplasm of pleura (163._)
Malignant neoplasm of thymus, heart, and mediastinum – heart (164.1)
Myeloid leukemia – acute (205.0_)
Hereditary hemolytic anemias – other thalassemia (282.49)
Sickle-cell disease (282.6_)
 | $6.03 | $5.13 | 96401 96409 96413 |
| clofarabine (Clolar)  | J9027 – injection, clofarabine, 1 mg | Lymphoid leukemia – acute (204.0_)
Myeloid leukemia – acute (205.0_)
Monocytic leukemia – acute (206.0_)
Acute erythema and erythroleukemia (207.0_)
Megalakaryocytic leukemia (207.2_)
Leukemia of unspecified cell type – acute (208.0_)
 | Myeloid leukemia – acute (205.0_)
Low-grade myelodysplastic syndrome lesions (238.72)
High-grade myelodysplastic syndrome lesions (238.73)
Myelodysplastic syndrome with 5q deletion (238.74)
Myelodysplastic syndrome, unspecified (238.75) | $135.00 | $116.35 | 96413 96415 |
| daunorubicin (Cerubidine) | J9150 – injection, daunorubicin, 10 mg | Lymphoid leukemia – acute (204.0_)
Myeloid leukemia – acute (205.0_)
Monocytic leukemia – acute (206.0_)
Acute erythema and erythroleukemia (207.0_)
Megalakaryocytic leukemia (207.2_)
Leukemia of unspecified cell type – acute (208.0_)
 | Malignant neoplasm of bone and articular cartilage (170._)
Malignant neoplasm of kidney and other and unspecified urinary organs – kidney, except pelvis (189.0)
Reticulosarcoma (200.0_)
Lymphosarcoma (200.1_)
Burkitt's tumor or lymphoma (200.2_)
Marginal zone lymphoma (200.3_)
Mantle cell lymphoma (200.4_)
Primary central nervous system lymphoma (200.5_)
Anaplastic large cell lymphoma (200.6_)
Large-cell lymphoma (200.7_)
Other named variants (200.8_)
Nodular lymphoma (202.0_)
Mycosis fungoides (202.1_)
Sézary's disease (202.2_)
Malignant histiocyteosis (202.3_)
Leukemic reticuloendotheliosis (202.4_)
Letterer-Siwe disease (202.5_)
Malignant mast cell tumors (202.6_)
Peripheral T-cell lymphoma (202.7_)
Other lymphomas (202.8_)
Other and unspecified malignant neoplasms of lymphoid and histiocytic tissue (202.9_)
Myeloid leukemia – chronic (205.1_)
 | $25.20 | $17.76 | 96409 96413 |
| decitabine (Dacogen)  | J0894 – injection, decitabine, 1 mg | Low-grade myelodysplastic syndrome lesions (238.72)
High-grade myelodysplastic syndrome lesions (238.73)
Myelodysplastic syndrome with 5q deletion (238.74)
Myelodysplastic syndrome, unspecified (238.75) | Lymphoid leukemia – acute (204.0_)
Myeloid leukemia – acute (205.0_)
Myeloid leukemia – chronic (205.1_)
<p>| $35.50 | $31.28 | 96413 96415 |
| degarelix (Firmagon) | J9155 – injection, degarelix, 1 mg | Malignant neoplasm of prostate (185) | N/A | $5.52 | $2.62 | 96402 |</p>
<table>
<thead>
<tr>
<th><strong>generic (Brand) Name</strong></th>
<th><strong>HCPCS Code – Code Description</strong></th>
<th><strong>FDA-Approved Uses</strong></th>
<th><strong>Compendia-Listed Off-Label Uses</strong></th>
<th><strong>Current Code Price (AWP-Based Pricing)</strong>*</th>
<th>**Medicare Allowable (ASP + 6%) **</th>
<th><strong>CPT® Admin Code(s)</strong></th>
</tr>
</thead>
</table>
| docetaxel (Taxotere)    | J9171 – injection, docetaxel, 1 mg | Malignant neoplasm of lip (140._)  
Malignant neoplasm of tongue (141._)  
Malignant neoplasm of major salivary glands (142._)  
Malignant neoplasm of gum (143._)  
Malignant neoplasm of floor of mouth (144._)  
Malignant neoplasm of other and unspecified parts of mouth (145._)  
Malignant neoplasm of oropharynx (146._)  
Malignant neoplasm of nasopharynx (147._)  
Malignant neoplasm of hypopharynx (148._)  
Malignant neoplasm of other and ill-defined sites within the lip, oral cavity, and pharynx (149._)  
Malignant neoplasm of stomach (151._)  
Malignant neoplasm of nasal cavities, middle ear, and accessory sinuses (160._)  
Malignant neoplasm of larynx (161._)  
Malignant neoplasm of trachea, bronchus, and lung (162._)  
Malignant neoplasm of female breast (174._)  
Malignant neoplasm of male breast (175._)  
Malignant neoplasm of prostate (185)  
Malignant neoplasm of other and ill-defined sites – head, face, and neck (195.0)  
Secondary and unspecified malignant neoplasm of lymph nodes – lymph nodes of head, face, and neck (196.0) | Malignant neoplasm of esophagus (150._)  
Malignant neoplasm of retroperitoneum and peritoneum – specified parts of peritoneum (158.8)  
Malignant neoplasm of retroperitoneum and peritoneum – unspecified (158.9)  
Malignant melanoma of skin (172._)  
Malignant neoplasm of ovary and other uterine adnexa (183._)  
Malignant neoplasm of other and unspecified female genital organs (184._)  
Malignant neoplasm of penis and other male genital organs (187._)  
Malignant neoplasm of bladder (188._)  
Malignant neoplasm of eye (190._)  
Malignant neoplasm without specification of site – disseminated (199.0)  
Malignant neoplasm without specification of site – other (199.1) | $24.71  
$18.43  
96413 |
| fludarabine (Fludara)   | J9185 – injection, fludarabine phosphate, 50 mg | Lymphoid leukemia – chronic (204.1._) | Reticulosarcoma (200.0._)  
Lymphosarcoma (200.1._)  
Burkitt’s tumor or lymphoma (200.2._)  
Marginal zone lymphoma (200.3._)  
Mantle cell lymphoma (200.4._)  
Primary central nervous system lymphoma (200.5._)  
Anaplastic large-cell lymphoma (200.6._)  
Large-cell lymphoma (200.7._)  
Other named variants (200.8._)  
Nodal lymphoma (202.0._)  
Mycosis fungoides (202.1._)  
Sezary’s disease (202.2._)  
Malignant histiocytosis (202.3._)  
Leukemic reticuloendotheliosis (202.4._)  
Letterer-Siwe disease (202.5._)  
Malignant mast cell tumors (202.6._)  
Peripheral T-cell lymphoma (202.7._)  
Other lymphomas (202.8._)  
Other and unspecified malignant neoplasms of lymphoid and histiocytic tissue (202.9._)  
Lymphoid leukemia – acute (204.0._)  
Myeloid leukemia – acute (205.0._)  
Low-grade myelodysplastic syndrome lesions (238.72)  
High-grade myelodysplastic syndrome lesions (238.73)  
Myelodysplastic syndrome with 5q deletion (238.74)  
Myelodysplastic syndrome, unspecified (238.75)  
Monoclonal paraproteinemia (273.1)  
Macroglobulinemia (273.3)  
Chronic glomerulonephritis – with lesion of membranes glomerulonephritis (582.1)  
Nephritis and nephropathy, not specified as acute or chronic – with lesion of membranes glomerulonephritis (583.1)  
Systemic lupus erythematosus (710.0)  
Enlargement of lymph nodes (785.6) | $285.16  
$92.43  
96413 |
<table>
<thead>
<tr>
<th>generic (Brand) Name</th>
<th>HCPCS Code – Code Description</th>
<th>FDA-Approved Uses</th>
<th>Compendia-Listed Off-Label Uses</th>
<th>Current Code Price (AWP-Based Pricing)*</th>
<th>Medicare Allowable (ASP + 6%) **</th>
<th>CPT® Admin Code(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>idarubicin (Idamycin)</td>
<td>J9211 – injection, idarubicin hydrochloride, 5 mg</td>
<td>Myeloid leukemia – acute (205.0_)</td>
<td>Reticulosarcoma (200.0_) Lymphosarcoma (200.1_) Burkitt’s tumor or lymphoma (200.2_) Marginal zone lymphoma (200.3_) Mantle cell lymphoma (200.4_) Primary central nervous system lymphoma (200.5_) Anaplastic large-cell lymphoma (200.6_) Large-cell lymphoma (200.7_) Other named variants (200.8_) Nodular lymphoma (200.9_) Mycosis fungoides (202.1_) Sézary’s disease (202.2_) Malignant histiocytosis (202.3_) Leukemic reticuloendotheliosis (202.4_) Letterer-Siwe disease (202.5_) Malignant mast cell tumors (202.6_) Peripheral T-cell lymphoma (202.7_) Other lymphomas (202.8_) Other and unspecified malignant neoplasms of lymphoid and histiocytic tissue (202.9_) Lymphoid leukemia – acute (204.0_) Lymphoid leukemia – chronic (204.1_) Myeloid leukemia – chronic (205.1_)</td>
<td>$300.00</td>
<td>$143.42</td>
<td>96409</td>
</tr>
<tr>
<td>nelarabine (Arranon)</td>
<td>J9261 – injection, nelarabine, 50 mg</td>
<td>Anaplastic large-cell lymphoma (200.6_) Other named variants (200.8_) Mycosis fungoides (202.1_) Sézary’s disease (202.2_) Peripheral T-cell lymphoma (202.7_) Other lymphomas (202.8_) Lymphoid leukemia – acute (204.0_)</td>
<td>Lymphoid leukemia – chronic (204.1_)</td>
<td>$131.32</td>
<td>$109.37</td>
<td>96413 96415</td>
</tr>
<tr>
<td>pegaspargase (Oncaspar)</td>
<td>J9266 – injection, pegaspargase, per single-dose vial</td>
<td>Lymphoid leukemia – acute (204.0_)</td>
<td>Reticulosarcoma (200.0_) Lymphosarcoma (200.1_) Burkitt’s tumor or lymphoma (200.2_) Marginal zone lymphoma (200.3_) Mantle cell lymphoma (200.4_) Primary central nervous system lymphoma (200.5_) Anaplastic large-cell lymphoma (200.6_) Large-cell lymphoma (200.7_) Other named variants (200.8_) Nodular lymphoma (200.9_) Mycosis fungoides (202.1_) Sézary’s disease (202.2_) Malignant histiocytosis (202.3_) Leukemic reticuloendotheliosis (202.4_) Letterer-Siwe disease (202.5_) Malignant mast cell tumors (202.6_) Peripheral T-cell lymphoma (202.7_) Other lymphomas (202.8_) Other and unspecified malignant neoplasms of lymphoid and histiocytic tissue (202.9_) Lymphoid leukemia – acute (204.0_) Lymphoid leukemia – chronic (204.1_) Myeloid leukemia – chronic (205.1_)</td>
<td>$3,280.00</td>
<td>$2,556.31</td>
<td>96401 96413 96415</td>
</tr>
<tr>
<td>trastuzumab (Herceptin)</td>
<td>J9355 – injection, trastuzumab, 10 mg</td>
<td>Malignant neoplasm of esophagus (150.1_) Malignant neoplasm of stomach (151.1_) Malignant neoplasm of female breast (174.1_) Malignant neoplasm of male breast (175.1_)</td>
<td>Malignant neoplasm of trachea, bronchus, and lung (162.1_) Malignant neoplasm of prostate (185.1_) Secondary malignant neoplasm of other specified sites – other parts of nervous system (198.4)</td>
<td>$80.61</td>
<td>$68.36</td>
<td>96413 96415</td>
</tr>
</tbody>
</table>

* The code price is based on the Healthcare Common Procedure Coding System (HCPCS) code description. HCPCS codes are a component of CMS (Centers for Medicare & Medicaid Services). The code price is an AWP-based pricing methodology developed by RJ Health Systems International, LLC, Wethersfield, Conn.
** Effective 1/1/11-3/31/11

Oncology-Related J-Code References
- HCPCS Level II Expert 2011
- Full prescribing information for each drug listed.
- CMS (Centers for Medicare & Medicaid Services) – Medicare-Allowable First Quarter – Effective Dates 1/1/11-3/31/11.
- Current code prices are effective as of 1/1/11.

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In advanced RCC:

**Change to Afinitor after initial VEGFR-TKI* failure (sunitinib or sorafenib)†**

- A different target from VEGFR-TKIs:
  - mTOR is an intracellular regulator downstream of VEGF\(^1,2\)
  - mTOR regulates both angiogenic and proliferative tumor progression pathways\(^1-4\)
  - Afinitor targets both tumor and blood vessel cells\(^1,3,5\)

- Adverse events are frequently class related and different from those seen with VEGFR-TKIs\(^2,6,7\)

For more information about Afinitor, call 1-888-4Afinitor (1-888-423-4648) or visit www.AFINITOR.com
For reimbursement questions, call 1-888-5AfiniTRAC (1-888-523-4648).

*VEGFR-TKI=vascular endothelial growth factor receptor tyrosine kinase inhibitor.
†Inhibition of mTOR by Afinitor has been shown to reduce cell proliferation, angiogenesis, and glucose uptake in in vitro and/or in vivo studies.

**Important Safety Information**

There have been reports of non-infectious pneumonitis and infections, some with fatal outcomes. Oral ulceration has been reported. Elevations of serum creatinine, glucose, lipids, and triglycerides and reductions of hemoglobin, lymphocytes, neutrophils, and platelets have been reported.

Please see Important Safety Information on right side of page.
Please see Brief Summary of full Prescribing Information on the following pages.
Afinitor is indicated for the treatment of patients with advanced renal cell carcinoma after failure of treatment with sunitinib or sorafenib.

**Important Safety Information**

Afinitor is contraindicated in patients with hypersensitivity to everolimus, to other rapamycin derivatives, or to any of the excipients.

Non-infectious pneumonitis is a class effect of rapamycin derivatives, including Afinitor. Fatal outcomes have been observed. If symptoms are moderate or severe, patients should be managed with dose interruption until symptoms improve or discontinuation, respectively. Corticosteroids may be indicated. Afinitor may be reintroduced at 5 mg daily depending on the individual clinical circumstances.

Afinitor has immunosuppressive properties and may predispose patients to bacterial, fungal, viral or protozoan infections, including infections with opportunistic pathogens. Localized and systemic infections, including pneumonia, other bacterial infections, invasive fungal infections, and viral infections including reactivation of hepatitis B virus have occurred. Some of these infections have been severe (e.g. leading to respiratory or hepatic failure) or fatal. Complete treatment of pre-existing invasive fungal infections prior to starting treatment. While taking Afinitor be vigilant for signs and symptoms of infection; if a diagnosis of infection is made, institute appropriate treatment promptly and consider interruption or discontinuation of Afinitor. If a diagnosis of invasive systemic fungal infection is made, discontinue Afinitor and treat with appropriate antifungal therapy.

Oral ulcerations (i.e. mouth ulcers, stomatitis, and oral mucositis) have occurred in patients treated with Afinitor. In such cases, topical treatments are recommended, but alcohol- or peroxide-containing mouthwashes should be avoided. Antifungal agents should not be used unless fungal infection has been diagnosed.

Elevations of serum creatinine, glucose, lipids, and triglycerides and reductions of hemoglobin, lymphocytes, neutrophils, and platelets have been reported in clinical trials. Renal function, hematological parameters, blood glucose, and lipids should be evaluated prior to treatment and periodically thereafter. When possible, optimal glucose and lipid control should be achieved before starting a patient on Afinitor.

Avoid concomitant use with strong CYP3A4 or PgP inhibitors. If co-administration with moderate CYP3A4 or PgP inhibitors is required, use caution and reduce dose of Afinitor to 2.5 mg daily. Increase the Afinitor dose if co-administered with a strong CYP3A4 inducer.

Afinitor should not be used in patients with severe hepatic impairment. Afinitor dose should be reduced to 5 mg daily for patients with moderate hepatic impairment.

The use of live vaccines and close contact with those who have received live vaccines should be avoided during treatment with Afinitor.

Fetal harm can occur if Afinitor is administered to a pregnant woman.

The most common adverse reactions (incidence ≥30%) were stomatitis (44%), infections (37%), asthenia (33%), fatigue (31%), cough (30%), and diarrhea (30%). The most common grade 3/4 adverse reactions (incidence ≥3%) were infections (9%), dyspnea (8%), fatigue (5%), stomatitis (4%), dehydration (4%), pneumonitis (4%), abdominal pain (3%), and asthenia (3%). The most common laboratory abnormalities (incidence ≥50%) were anemia (92%), hypercholesterolemia (77%), hypertriglyceridemia (73%), hyperglycemia (57%), lymphopenia (51%), and increased creatinine (50%). The most common grade 3/4 laboratory abnormalities (incidence ≥3%) were lymphopenia (18%), hyperglycemia (16%), anemia (13%), hypophosphatemia (6%), and hypercholesterolemia (4%). Deaths due to acute respiratory failure (0.7%), infection (0.7%), and acute renal failure (0.4%) were observed on the Afinitor arm.


**AFINITOR®**

(everolimus) tablets

2.5 mg | 5 mg | 10 mg

**Change tracks**

Novartis Oncology

Novartis Pharmaceuticals Corporation
East Hanover, NJ 07936 ©2010 Novartis

Printed in U.S.A. 08/10 C-AFI-100066
AFINITOR® (everolimus) tablets for oral administration

BRIEF SUMMARY: Please see package insert for full prescribing information.

1 INDICATIONS AND USAGE
AFINITOR® is indicated for the treatment of patients with advanced renal cell carcinoma after failure of treatment with sunitinib or sorafenib.

4 CONTRAINDICATIONS
Hypersensitivity to the active substance, to other rapamycin derivatives, or to any of the excipients. Hypersensitivity reactions manifested by symp- toms including, but not limited to, anaphylaxis, dyspnea, flushing, chest pain, or angioedema (e.g., swelling of the airways or tongue, with or without respiratory impairment) have been observed with everolimus and other rapamycin derivatives.

5 WARNINGS AND PRECAUTIONS
5.1 Non-infectious Pneumonitis
Non-infectious pneumonitis is a class effect of rapamycin derivatives, including AFINITOR. In the randomized study, non-infectious pneumonitis was reported in 14% of patients treated with AFINITOR. The incidence of Common Toxicity Criteria (CTC) grade 3 and 4 non-infectious pneumonitis was 4% and 0%, respectively [see Adverse Reactions (6.1)]. Fatal outcomes have been observed.

5.2 Infections
AFINITOR has immunosuppressive properties and may predispose patients to bacterial, fungal, viral, or protozoan infections, including infections with opportunistic pathogens [see Adverse Reactions (6.1)]. Localized and systemic infections, including pneumonia, other bacterial infections, invasive fungal infections, such as aspergillosis or candidiasis, and viral infections including reactivation of hepatitis B virus have occurred in patients taking AFINITOR. Some of these infections have been severe (e.g., leading to respiratory or hepatic failure) or fatal. Physicians and patients should be aware of the increased risk of infection with AFINITOR. Complete treatment of pre-existing invasive fungal infections prior to starting treatment with AFINITOR. While taking AFINITOR be vigilant for signs and symptoms of infection; if a diagnosis of an infection is made, institute appropriate treatment promptly and consider interruption or discontinuation of AFINITOR. If a diagnosis of invasive systemic fungal infection is made, discontinue AFINITOR and treat with appropriate antifungal therapy.

5.3 Oral Ulceration
Mouth ulcers, stomatitis, and oral mucositis have occurred in patients treated with AFINITOR. In the randomized study, approximately 44% of AFINITOR-treated patients developed mouth ulcers, stomatitis, or oral mucositis, which were mostly CTC grade 1 and 2 [see Adverse Reactions (6.1)]. In such cases, topical treatments are recommended, but alcohol-or peroxide-containing mouthwashes should be avoided as they may exacerbate the condition. Antifungal agents should not be used unless fungal infection has been diagnosed [see Drug Interactions (7.1)].

5.4 Laboratory Tests and Monitoring

5.4.1 Renal Function
Elevations of serum creatinine, usually mild, have been reported in clinical trials [see Adverse Reactions (6.1)]. Monitoring of renal function, including measurement of blood urea nitrogen (BUN) or serum creatinine, is recommended prior to the start of AFINITOR therapy and periodically thereafter.

5.4.2 Blood Glucose and Lipids
Hyperglycemia, hyperlipidemia, and hypertriglyceridemia have been reported in clinical trials [see Adverse Reactions (6.1)]. Monitoring of fasting serum glucose and lipid profile is recommended prior to the start of AFINITOR therapy and periodically thereafter. When possible, optimal glucose and lipid control should be achieved before starting a patient on AFINITOR.

5.5 Drug-drug Interactions
Due to significant increases in exposure of everolimus, co-administration with strong inhibitors of CYP3A4 (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, nefazodone, saquinavir, telithromycin, ritonavir, indinavir, nelfinavir, voriconazole) or P-glycoprotein (PgP) should be avoided. Grapefruit, grapefruit juice and other foods that are known to affect cytochrome P450 and PgP activity should also be avoided during treatment [see Dosage and Administration (2.2) in the full prescribing information and Drug Interactions (7.1)].

A reduction of the AFINITOR dose is recommended when co-administered with a moderate CYP3A4 inhibitor (e.g., amphotericin B, ketoconazole, ritonavir, saquinavir, itraconazole or P-glycoprotein (PgP) inhibitor [see Dosage and Administration (2.2) in the full prescribing information and Drug Interactions (7.1)].

An increase in the AFINITOR dose is recommended when co-administered with a strong CYP3A4 inducer (e.g., St. John’s Wort (Hypericum perforatum), dexamethasone, prednisone, prednisolone, phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital) [see Dosage and Administration (2.2) in the full prescribing information and Drug Interactions (7.2)].

5.6 Hepatic Impairment
The safety and pharmacokinetics of AFNITOR were evaluated in a study in eight patients with moderate hepatic impairment (Child-Pugh class B) and eight subjects with normal hepatic function. Exposure was increased in patients with moderate hepatic impairment, therefore a dose reduction is recommended.

AFINITOR has not been studied in patients with severe hepatic impairment (Child-Pugh class C) and should not be used in this population [see Dosage and Administration (2.2) in the full prescribing information and Use in Specific Populations (8.7)].

5.7 Vaccinations
The use of live vaccines and close contact with those who have received live vaccines should be avoided during treatment with AFINITOR. Examples of live vaccines are: intranasal influenza, measles, mumps, rubella, oral polio, BCG, yellow fever, varicella, and TY21a typhoid vaccines.

5.8 Use in Pregnancy
Pregnancy Category D
There are no adequate and well-controlled studies of AFINITOR in pregnant women. However, based on mechanism of action, AFINITOR may cause fetal harm when administered to a pregnant woman. Everolimus caused embryo-fetal toxicities in animals at maternal exposures that were lower than human exposures at the recommended dose of 10 mg daily. If this drug is used during pregnancy or if the patient becomes pregnant while taking the drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to use an effective method of contraception while taking AFINITOR and for up to 8 weeks after ending treatment [see Use in Specific Populations (8.1)].

6 ADVERSE REACTIONS
The following serious adverse reactions are discussed in greater detail in another section of the label:
- Non-infectious pneumonitis [see Warnings and Precautions (5.1)]
- Infections [see Warnings and Precautions (5.2)]

6.1 Clinical Studies Experience
Because clinical trials are conducted under widely varying conditions, the adverse reaction rates observed cannot be directly compared to rates in other trials and may not reflect the rates observed in clinical practice.

The data described below reflect exposure to AFINITOR (n=274) and placebo (n=137) in a randomized, controlled trial in patients with metastatic renal cell carcinoma who received prior treatment with sunitinib and/or sorafenib. The median age of patients was 61 years (range 27-85), 88% were Caucasian, and 78% were male. The median duration of blinded study treatment was 141 days (range 19-451) for patients receiving AFINITOR and 60 days (range 21-235) for those receiving placebo.

The most common adverse reactions (incidence ≥30%) were stomatitis, infections, anemia, fatigue, cough, and diarrhea. The most common grade 3/4 adverse reactions (incidence ≥3%) were infections, diarrhea, fatigue, stomatitis, dehydration, pneumonitis, abdominal pain, and anemia.

The most common laboratory abnormalities (incidence ≥50%) were anemia,
hypertriglyceridemia, hyperglycemia, lymphopenia, and increased creatinine. The most common grade 3/4 laboratory abnormalities (incidence ≥3%) were lymphopenia, hyperglycemia, anemia, hypophosphatemia, and hypercholesterolemia. Deaths due to acute respiratory failure (0.7%), infection (0.7%) and acute renal failure (0.4%) were observed during the AFINITOR arm but none on the placebo arm. The most common treatment-emergent adverse events (irrespective of causality) were pneumonitis and dyspnea. Infections, stomatitis, and pneumonitis were the most common reasons for treatment discontinuation due to AFINITOR treatment were for infections, anemia, and stomatitis.

Table 1 compares the incidence of treatment-emergent adverse reactions reported with an incidence of ≥10% for patients receiving AFINITOR 10 mg daily versus placebo. Within each MedDRA system organ class, the adverse reactions are presented in order of decreasing frequency.

Table 1: Adverse Reactions Reported in at least 10% of Patients and at a Higher Rate in the AFINITOR Arm than in the Placebo Arm

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>AFINITOR 10 mg/day</th>
<th>Placebo</th>
<th>N=274</th>
<th>N=137</th>
</tr>
</thead>
<tbody>
<tr>
<td>All grades                                            97</td>
<td>52</td>
<td>13</td>
<td>23</td>
<td>5</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stomatitis&lt;sup&gt;a&lt;/sup&gt;</td>
<td>44</td>
<td>&lt;1</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>30</td>
<td>50</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>26</td>
<td>10</td>
<td>19</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>20</td>
<td>20</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Infections and Infestations&lt;sup&gt;b&lt;/sup&gt;</td>
<td>37</td>
<td>12</td>
<td>18</td>
<td>1</td>
</tr>
<tr>
<td>General Disorders and Administration Site Conditions</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthenia</td>
<td>33</td>
<td>3</td>
<td>&lt;1</td>
<td>23</td>
</tr>
<tr>
<td>Fatigue</td>
<td>31</td>
<td>50</td>
<td>27</td>
<td>3</td>
</tr>
<tr>
<td>Edema peripheral</td>
<td>25</td>
<td>&lt;1</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>20</td>
<td>&lt;1</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>Mucosal inflammation</td>
<td>19</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Respiratory, Thoracic and Mediastinal Disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>30</td>
<td>&lt;1</td>
<td>0</td>
<td>16</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>24</td>
<td>6</td>
<td>1</td>
<td>15</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>18</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Pneumonitis&lt;sup&gt;c&lt;/sup&gt;</td>
<td>14</td>
<td>4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Skin and Subcutaneous Tissue Disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>29</td>
<td>1</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>Pruritus</td>
<td>14</td>
<td>&lt;1</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>Dry skin</td>
<td>13</td>
<td>&lt;1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Metabolism and Nutrition Disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anorexia</td>
<td>26</td>
<td>1</td>
<td>0</td>
<td>14</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>19</td>
<td>&lt;1</td>
<td>&lt;1</td>
<td>9</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>10</td>
<td>0</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Musculoskeletal and Connective Tissue Disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>10</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Median Duration of Treatment (d)</td>
<td>141</td>
<td>60</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CTCAE Version 3.0

<sup>a</sup>Stomatitis (including aphthous stomatitis), and mouth and tongue ulceration. Includes all preferred terms within the ‘infections and infestations’ system organ class, the most common being nasopharyngitis (6%), pneumonia (6%), urinary tract infection (5%), bronchitis (4%), and sinusitis (3%), and also including aspergillosis (<1%), candidiasis (<1%), and sepsis (<1%).

Information from further clinical trials

In clinical trials, everolimus has been associated with serious cases of hepatitis B reactivation, including fatal outcomes.

7. DRUG INTERACTIONS

Everolimus is a substrate of CYP3A4, and also a substrate and moderate inhibitor of the multidrug efflux pump Pgp. In vitro, everolimus is a competitive inhibitor of CYP3A4 and a mixed inhibitor of CYP2D6.

7.1 Agents that may Increase Everolimus Blood Concentrations

CYP344 Inhibitors and PgP Inhibitors: In healthy subjects, compared to AFINITOR treatment alone there were significant increases in everolimus exposure when AFINITOR was coadministered with:

- ketoconazole (a strong CYP344 inhibitor and a PgP inhibitor) - C<sub>min</sub> and AUC increased by 3.9- and 15.0-fold, respectively.
- erthyromycin (a moderate CYP344 inhibitor and a PgP inhibitor) - C<sub>min</sub> and AUC increased by 2.0- and 4.4-fold, respectively.
- verapamil (a moderate CYP344 inhibitor and a PgP inhibitor) - C<sub>min</sub> and AUC increased by 2.3- and 3.5-fold, respectively.

Concomitant strong inhibitors of CYP344 and PgP should not be used [see Warnings and Precautions (5.5)].

Use caution when AFINITOR is used in combination with moderate CYP344 or PgP inhibitors. If alternative treatment cannot be administered reduce the AFINITOR dose. [See Dosage and Administration (2.2) in the full prescribing information]

7.2 Agents that may Decrease Everolimus Blood Concentrations

CYP344 Inducers: In healthy subjects, co-administration of AFINITOR with rifampin, a strong inducer of CYP344, decreased everolimus AUC and C<sub>min</sub> by 64% and 58% respectively, compared to everolimus treatment alone. Consider a dose increase of AFINITOR when co-administered with
strong inducers of CYP3A4 (e.g., dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, phenobarbital) or Pgp if alternative treatment cannot be administered. St. John’s Wort may decrease everolimus exposure unpredictably and should be avoided [see Dosage and Administration (2.2) in the full prescribing information].

7.3 Agents whose Plasma Concentrations may be Altered by Everolimus

Studies in healthy subjects indicate that there are no clinically significant pharmacokinetic interactions between AFINITOR and the HMG-CoA reductase inhibitors atorvastatin (a CYP3A4 substrate) and pravastatin (a non-CYP3A4 substrate) and population pharmacokinetic analyses also detected no influence of simvastatin (a CYP3A4 substrate) on the clearance of AFINITOR.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D [see Warnings and Precautions (5.8)]

There are no adequate and well-controlled studies of AFINITOR in pregnant women. However, based on mechanism of action, AFINITOR may cause fetal harm when administered to a pregnant woman. Everolimus caused embryo-fetal toxicities in animals at maternal exposures that were lower than human exposures at the recommended dose of 10 mg daily. If this drug is used during pregnancy or if the patient becomes pregnant while taking the drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to use an effective method of contraception while receiving AFINITOR and for up to 8 weeks after ending treatment.

In animal reproductive studies, oral administration of everolimus to female rats before mating and through organogenesis induced embryofetal toxicities, including increased resorption, pre-implantation and post-implantation loss, decreased numbers of live fetuses, malformation (e.g., sternal cleft) and retarded skeletal development. These effects occurred in the absence of maternal toxicities. Embryo-fetal toxicities occurred at approximately 4% the exposure (AUC0-24h) in patients receiving the recommended dose of 10 mg daily. In rabbits, embryotoxicity evident as an increase in resorptions occurred at an oral dose approximately 1.6 times the recommended human dose on a body surface area basis. The effect in rabbits occurred in the presence of maternal toxicities.

In a pre- and post-natal development study in rats, animals were dosed from implantation through lactation. At approximately 10% of the recommended human dose based on body surface area, there were no adverse effects on delivery and lactation and there were no signs of maternal toxicity. However, there was reduced body weight (up to 9% reduction from the control) and slight reduction in survival in offspring (-5% died or missing). There were no drug-related effects on the developmental parameters (morphological development, motor activity, learning, or fertility assessment) in the offspring.

Doses that resulted in embryo-fetal toxicities in rats and rabbits were ≥0.1 mg/kg (0.6 mg/m²) and 0.8 mg/kg (9.6 mg/m²), respectively. The dose in the pre- and post-natal development study in rats that caused reduction in body weights and survival of offspring was 0.1 mg/kg (0.6 mg/m²).

8.3 Nursing Mothers

It is not known whether everolimus is excreted in human milk. Everolimus and/or its metabolites passed into the milk of lactating rats at a concentration 3.5 times higher than in maternal serum. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from everolimus, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

The safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

In the randomized study, 41% of AFINITOR-treated patients were ≥65 years in age, while 7% percent were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out [see Clinical Pharmacology (12.3) in the full prescribing information].

No dosage adjustment is required in elderly patients [see Clinical Pharmacology (12.3) in the full prescribing information].

8.6 Renal Impairment

No clinical studies were conducted with AFINITOR in patients with decreased renal function. Renal impairment is not expected to influence drug exposure and no dosage adjustment of everolimus is recommended in patients with renal impairment [see Clinical Pharmacology (12.3) in the full prescribing information].

8.7 Hepatic Impairment

For patients with moderate hepatic impairment (Child-Pugh class B), the dose should be reduced to 5 mg daily [see Dosage and Administration (2.2) in the full prescribing information, Warnings and Precautions (5.6) and Clinical Pharmacology (12.3) in the full prescribing information].

The impact of severe hepatic impairment (Child-Pugh class C) has not been assessed and use in this patient population is not recommended [see Warnings and Precautions (5.6)].

10 OVERDOSAGE

In animal studies, everolimus showed a low acute toxic potential. No lethality or severe toxicity were observed in either mice or rats given single oral doses of 2000 mg/kg (limit test).

Reported experience with overdose in humans is very limited. Single doses of up to 70 mg have been administered. The acute toxicity profile observed with the 70 mg dose was consistent with that for the 10 mg dose.

16 STORAGE

Store AFINITOR (everolimus) tablets at 25°C (77°F); excursions permitted between 15°-30°C (59°-86°F). [See USP Controlled Room Temperature.] Store in the original container; protect from light and moisture. Keep this and all drugs out of the reach of children.

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published. AFINITOR tablets should not be crushed. Do not take tablets which are crushed or broken.

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Novartis Pharma Stein AG
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Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936

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A Discussion with Kevin Kobielski, CPA
Director, Pharmacy Services, HealthNow New York Inc.

Managing injectables can be a daunting task, especially considering the generally high price tag of these therapies and the multifaceted approach necessary for controlling costs and improving quality in this area.

While payors vary in their strategies for achieving this end, their successes and pitfalls offer key learnings for optimizing outcomes.

HealthNow New York Inc. is the leading healthcare company in western New York. Since 1936, HealthNow has provided a full spectrum of healthcare services and innovative funding arrangements enhanced by value-added services for plan members. ManagedCare Oncology recently sat down with Kevin Kobielski, CPA, Director, Pharmacy Services, HealthNow New York Inc., to gain insights on his plan’s integrated strategy for managing injectables and the challenges he has encountered along the way.

MCO: Tell us about how you inherited the task of managing injectable products.

Kevin Kobielski: As part of my initial evaluation after taking over the pharmacy department, I realized we did not have the appropriate focus...
managed care oncology Quarter 1 2011

on our injectable spend. Historically, it was managed along with the other expenditures on the medical side and had always taken a backseat to other initiatives that had greater visibility and financial impact. Since our department was already responsible for the utilization management of these drugs, it made sense to have accountability for the entire spend. So we really adopted the responsibility about a year ago and have been aggressively managing it ever since.

**MCO:** What was your approach to identifying injectable drug cost-management opportunities?

**Kevin Kobielski:** The first thing we did was take a really close look at our current contracts with specialty vendors. I’m sure we’re similar to other health plans in that we have multiple vendors covering multiple channels. So taking an inventory and evaluating whether we had the appropriate contracts in place was a key step. We also hired a consultant with an extremely deep knowledge base in specialty management to do an assessment of our current state. Given the extreme complexity of the area, getting an assessment done by someone who has the complete picture is essential.

**MCO:** How do you prioritize opportunities?

**Kevin Kobielski:** At any health plan, appropriate use and cost are key drivers, so you’re looking for areas where you get the most bang for your buck. We have a corporate initiative that is dedicated to identifying areas of cost savings. A key piece of that initiative in 2011 will be savings related to injectable management. So we tend to focus resources on the projects that result in the highest return on investment (ROI).

**MCO:** What advice can you give someone who has just inherited injectable management?

**Kevin Kobielski:** The key success factor is bringing together all the key stakeholders and developing a comprehensive strategy. Since you’re dealing with a highly complex subject that touches multiple areas of the company, getting a team together that has representation from affected areas is important. You need the clinicians to determine the appropriate policy, you need the network to ensure proper reimbursement, and you need legal involved to ensure the appropriate contracts are in place. There are so many different factors to consider: rebates, pharmacy benefit management (PBM) contracting, and reimbursement methodology, just to name a few. And all these factors are intertwined, so your strategy needs to be robust and flexible.

**MCO:** What is the biggest challenge for someone who is embarking on building an injectable management strategy?

**Kevin Kobielski:** The sheer complexity of what we’re dealing with in injectable management is probably the biggest challenge. Multiple specialty pharmacies, multiple distribution channels, physician reimbursement methodologies, channel management interventions for reimbursing in alternative settings, pipeline management, pricing ... it’s such a complex environment that it’s a challenge just looking at how all the pieces fit together. It’s like a balloon: When you push on one side, the other side pops out. For example, you have to think about what you need to do on the drug administration side to ease the pain of taking a bite out of the drug margin. To achieve this, you need to get all the different players together and seek feedback from other areas within the plan.

**MCO:** What initiatives will you put in place to manage medical benefit injectable costs, particularly oncology expenses, in 2011?

**Kevin Kobielski:** We’re restructuring all our specialty vendor contracts to ensure appropriate contract terms and pricing. We’re also implementing a new physician reimbursement methodology that promotes the use of generics and moves us away from average wholesale price (AWP) as our reimbursement benchmark. In addition, we’re taking a look at all our clinical policies to ensure we have policies on the correct drugs and the criteria are appropriate.
Since you’re balancing clinical considerations along with financial ones, you need to make sure that you think these things through.

We’re also working on a comprehensive preferred product strategy, which maximizes our rebate dollars where appropriate. Our decisions related to preferred products take into consideration many factors, but if we can lower the overall cost of treatment by taking advantage of rebates without sacrificing quality, it’s a win-win.

**MCO:** Can you describe, at a high level, how these initiatives are being operationalized?

**Kevin Kobielski:** Unfortunately, we were behind the eight ball and trying to do a lot at once. In order to operationalize all these different initiatives, we sought resources from our project management area to assist. The project management office has helped tremendously in moving these initiatives forward and putting the appropriate discipline around their implementation. The project management resource works with my team and the other subject matter experts across the company to ensure these projects get done. Since everybody usually has his or her day job, having someone whose sole focus is project implementation is extremely valuable.

**MCO:** Can you tell us what challenges you expect moving forward?

**Kevin Kobielski:** I believe the biggest challenge is trying to stay out in front of all drugs coming down the pipeline and trying to figure out what will comprise the next generation in cost-management strategies. As costs continue to rise, we are going to have to come up with innovative ways to keep them down.

**MCO:** What are the most likely things that may delay implementation?

**Kevin Kobielski:** Allocation of resources is the single biggest factor in the timely implementation of our programs. Just like any other health plan, we are trying to do a lot with limited resources, so ensuring we focus our limited resources on what is going to give us the highest ROI is key.

**MCO:** What are your plan’s goals for these initiatives?

**Kevin Kobielski:** There are financial targets and timelines for each initiative, and the two are tied together. The financial impact while preserving or improving quality of care is ultimately what drives us. Like any health plan, we have limited resources, so the goal is getting the most out of them. I have a lot of control over what we’re putting our pharmacy resources toward, so that assists in the whole process. I have a team of pharmacists that report to me, so I can get them allocated to projects for timely achievement of these goals.

It’s obviously not all financial, though. We want the member to get the appropriate drug at the appropriate time, and we’re not trying to restrict access to appropriate therapies. But we do want to make sure therapies are utilized prudently with financial considerations taken into account.
**MCO:** How are you planning to measure whether the initiatives are successful or not?

**Kevin Kobielski:** Again, the financial data are key. But we also want to know if we met our financial goals while maintaining the quality of care and without disrupting our physician network. We want a spirit of collaboration among our physicians, and we definitely don’t want to damage those relationships.

**MCO:** What background experiences do you believe helped you become successful in developing an injectable management program?

**Kevin Kobielski:** I believe that having a diverse background that gives you exposure to all aspects of managed care is extremely helpful in implementing change in such a complex environment. Running this department is similar to running a small company. Just focusing on the clinical aspects is not enough. There are operational and financial factors that have to be considered to ensure the goals of this department are achieved.

You also have to be humble and realize that you don’t always have all the answers, and you need to seek input from all your staff. Your staff is an extremely valuable resource, and making sure they are engaged in the process is important.

**MCO:** You get to fix one thing to improve your plan’s ability to manage oncology costs – what would you want to change?

**Kevin Kobielski:** Our physician reimbursement methodology. The current system we’re using is outdated, with a cost-plus methodology based on AWP, so costs rise dramatically every year with rising drug costs. I’d like to change this so that physicians are reimbursed appropriately and we provide the appropriate incentive to utilize generic medications. Physicians have financial goals as well, so to take that financial component out of the equation is naïve.

I’d also like to see more transparency of data on the medical side and change the way we get data from the medical side. We’re already doing a lot of work compiling a set of reports around our specialty spend so that we can implement programs to achieve change at that level.

**MCO:** How should payors measure cost-of-care changes?

**Kevin Kobielski:** Obviously, on the physician reimbursement side, you have to look at not only the drug reimbursement, but also drug administration fees. You have to take into consideration the entire physician reimbursement methodology. You need to make sure your program dovetails with that methodology nicely. In measuring cost of care, what you’re trying to get to is the outcomes. When you achieve appropriate care, it will ideally decrease both the medical and pharmacy spends. You have to look at everything through a global optic, and health plans are uniquely positioned to do so. They can integrate medical and pharmacy data, look at HEDIS data, etc. Health plans have all this information at their fingertips, putting them in position to take a comprehensive look at the big picture.

**MCO:** What advice can you give to stakeholders at regional plans who are just now developing their oncology management strategies?

**Kevin Kobielski:** The key thing here – since it’s a growing issue with the pipeline looking the way it does now – is to dedicate the resources to it. This is not a part-time job. You need to have a resource entirely dedicated to injectable management. That’s where we fall short sometimes. With any plan, resources are tight, and you want to keep premiums as low as possible. However, you must work with your clinicians to manage spend, and you need resources to do that. Ultimately, you need to invest those resources to truly “bend the trend.”
Specialty Pharmacy Management

As your specialty pharmacy partner, ICORE Healthcare delivers strategic solutions to reduce specialty pharmaceutical costs and improve outcomes for your members. Our integrated approach focuses on the key drivers of specialty drug spend, which have resulted in significant savings for our customers.

HIGHLIGHTS
When you partner with ICORE, for specialty pharmacy management, you can expect:

• A specialty pharmacy program that compares favorably to traditional models, but is set apart by integration with our formulary optimization.
• An approach that is considered reasonable, strategic, and thoughtful within the oncology community. We support “buy and bill” and place an emphasis on generics and least-cost alternatives to reduce drug carrying costs.
• Significant cost savings by moving market share and maximizing cost effectiveness without burdening your resources.
• Annual savings of 10% to 15% that begin within 30–90 days of entering into a partnership.
• A variable fee schedule that doesn’t have the pitfalls of either AWP- or ASP-based methods.
• Best-in-class rebate contracts that ensure you have the best available terms.

SOLUTIONS
ICORE offers tailored solutions for managing the entire continuum of the specialty drug spend, including pharmacy and medical drug components, as well as oncology:

• Formulary Management—Prefers lowest net cost product in key biotech classes, offers access to best of class national injectable formulary and has a proven record of optimizing formulary contracts for preferred, lower cost drugs.
• Distribution and Conversion—Our specialty pharmacy conversion program amplifies contract performance and formulary adherence through product preferencing.
• Oncology Management—Our clinical experience helps to ensure patients receive the most appropriate care and our operational capabilities reduce program costs by preventing claims errors, improving payor operations and rationalizing payments using clinically accepted standards.

VALUE
ICORE brings payors, drug manufacturers, providers, patients and pharmacies together around the right specialty injectable drugs, doses and frequencies to maximize effectiveness and minimize costs.
Title: Randomized, phase 3 trial of panitumumab with infusional fluorouracil, leucovorin, and oxaliplatin (FOLFOX4) vs. FOLFOX4 alone as first-line treatment in patients with previously untreated metastatic colorectal cancer: the PRIME study.


Purpose: Colorectal cancer is the third most common cancer among men and women in the U.S. with approximately 175,000 new cases yearly. The epidermal growth factor receptor (EGFR) has proven to be a clinically meaningful target for monoclonal antibodies (mABs) in all lines of treatment for metastatic colorectal cancer (mCRC). Panitumumab (Vectibix) is a fully humanized mAB that targets the EGFR. Initial studies have shown its efficacy as monotherapy for patients with chemotherapy-refractory mCRC. This study evaluates the safety and efficacy of panitumumab when added to FOLFOX4 as initial therapy for mCRC.

Methods: Patients 18 and older with previously untreated mCRC with an ECOG (Eastern Cooperative Oncology Group) performance status of 0 to 2 were eligible for inclusion. Fluorouracil- (Adrucil) based chemotherapy was allowed in the adjuvant setting if disease recurrence occurred at least six months following its completion. Fluorouracil- (Adrucil) based chemotherapy was allowed in the adjuvant setting if disease recurrence occurred at least six months following its completion. Patients were randomized according to their KRAS status and assigned 1:1 to receive either panitumumab-FOLFOX4 or FOLFOX4 alone. Panitumumab was administered intravenously (IV) over one hour at a dose of 6 mg/kg every two weeks prior to FOLFOX4 therapy. If tolerated, subsequent doses were administered over 30 minutes. FOLFOX4 consisted of oxaliplatin (Eloxatin) 85 mg/m² IV on day one and leucovorin 200 mg/m² IV infusion followed by fluorouracil 400 mg/m² IV bolus and 600 mg/m² as a 22-hour continuous infusion on days one and two. Cycles were repeated every two weeks. The primary objective of the study was to assess the effect of the addition of panitumumab to FOLFOX4 on progression-free survival (PFS) as initial therapy for mCRC with wild type (WT) KRAS tumors and in patients with mutant (MT) tumors. Secondary endpoints included overall survival (OS) and safety.

Results: One-thousand one-hundred and eighty-three patients (1,183) were randomly assigned; KRAS results were available in 93%. For patients with WT KRAS, the combination of panitumumab-FOLFOX4 showed a significant improvement in PFS when compared with FOLFOX4 alone (9.6 months vs. 8.0 months; p = 0.02). PFS was inferior in patients receiving panitumumab-FOLFOX4 vs. FOLFOX4 alone in those patients with MT KRAS (7.3 months vs. 8.8 months). In the WT KRAS arm, the median OS was 23.9 months for panitumumab-FOLFOX4 and 19.7...
months in the FOLFOX4 arm (p = 0.72). For those patients with MT KRAS, median OS was 15.5 months if treated with panitumumab-FOLFOX4 and 19.3 months if treated with FOLFOX4 (p = 0.068). As expected, skin toxicity commonly seen with drugs affecting the EGFR was more common in patients treated with panitumumab.

**Conclusion:** The study demonstrates that panitumumab-FOLFOX4 was well tolerated and significantly improved PFS in patients with WT KRAS tumors, which underscores the importance of KRAS testing in patients with mCRC.

**Managed Care Implications:**
Panitumumab-FOLFOX4 offers another treatment option for patients with mCRC receiving initial chemotherapy for advanced disease. KRAS testing is critical in determining who will have the highest probability of responding to this combination. Other molecular targets, such as BRAF, may also be found to play a role in determining optimal therapy for these patients.

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**Title:** Identification of potentially responsive subsets when cetuximab is added to oxaliplatin-fluoropyrimidine chemotherapy (CT) in first-line advanced colorectal cancer (aCRC): mature results from the MRC COIN trial.

**Authors:** Maughan TS, Adams R, Smith CG, et al.

**Reference:** *J Clin Oncol.* 2010;28(15s) (suppl; abstract 3502).

**Purpose:** More than 16,000 patients a year succumb to mCRC in the U.K. Therapy to this time has centered around the use of an oxaliplatin (Eloxatin) and fluoropyrimidine (Xeloda, Adrucil) based chemotherapy. Cetuximab (Erbitux) binds specifically to the EGFR on the tumor cell, as well as on normal cells, and inhibits the binding of EGFR and other ligands. This blocks phosphorylation and activation of receptor-associated kinases, resulting in inhibition of cell growth and induction of apoptosis (scheduled cell death). It is indicated for second-line therapy in patients with aCRC. This study evaluates the drug in the first-line setting.

**Methods:** Patients with measurable, inoperable aCRC were eligible for the trial if they had not received chemotherapy for metastatic disease. They had a World Health Organization (WHO) performance status of 0 to 2 and adequate end-organ function. Patients were randomized to receive either oxaliplatin and fluorouracil (OxFU) as well as leucovorin every two weeks or oxaliplatin and capecitabine (CapeOX) as well as leucovorin every three weeks (arm A), or one of the same combinations with weekly cetuximab (arm B). The primary outcome was the OS in those patients with WT KRAS disease.

**Results:** One-thousand six-hundred and thirty (1,630) patients were accrued; 66% received CapeOX and 34% were treated with OxFU. Patient tumors that contained WT KRAS were 55%. There was no difference in the two-year OS between the two arms of the study. Those treated on arm A had a 40% survival and those treated on arm B with cetuximab had a two-year survival of 38.8%. PFS also did not differ between the two treatment arms.

**Conclusion:** The addition of cetuximab to oxaliplatin-based chemotherapy did not improve OS or PFS in WT KRAS patients.

**Managed Care Implications:** These findings are in direct conflict with the first trial presented as to the role of EGFR inhibitors in combination with chemotherapy as first-line therapy for patients with aCRC. Additional studies will need to be completed to better identify which patients will benefit from the addition of an EGFR inhibitor as first-line therapy for aCRC.
Title: Multicenter, randomized phase 2 trial of bevacizumab plus folinic acid, fluorouracil, gemcitabine (FFG) vs. bevacizumab plus folinic acid, fluorouracil, oxaliplatin (FOLFOX4) as first-line therapy for patients with advanced colorectal cancer.


Purpose: Despite screening methods and an increase in public awareness, colorectal cancer remains the third most common malignancy diagnosed in the U.S. Advances in therapy over the past 20 years have led to incremental improvement in OS for patients with advanced disease. Unfortunately, nearly all patients with aCRC will succumb to their disease, proving there is still a need for the development of new agents and combinations with activity in this disease. Therapy for aCRC has involved the use of 5-fluorouracil (5-FU, Aucrul) in combination with folinic acid (FA, calcium leucovorin). A number of other agents have been added to this combination in an attempt to increase OS. This includes irinotecan (Camptosar) and oxaliplatin (Eloxatin). The oxaliplatin combination with 5-FU/FA (FOLFOX4) has been shown to have superior efficacy over the irinotecan, 5-FU/FA (IFL) combination and has less toxicity. Gemcitabine (Gemzar), a pyrimidine nucleoside antimetabolite, has demonstrated in vitro activity in colorectal cancer cell lines, but it has shown no activity as a single agent in the treatment of the disease. It is, however, believed to potentiate the antitumor activity of 5-FU as a biomodulator of the interaction of 5-FU and thymidylate synthetase. Activity has been seen with the combination in phase 1 dose-finding studies. Bevacizumab (Avastin) is a recombinant humanized monoclonal antibody that inhibits vascular endothelial growth factor (VEGF) receptor-mediated intracellular signaling. It is approved for first-line therapy for the treatment of aCRC in combination with 5-FU-based chemotherapy. This study compares FFG and FOLFOX4 in patients who had not received chemotherapy for advanced disease.

Methods: Patients with unresectable stage III or IV adenocarcinoma of the colon or rectum were eligible. Prior adjuvant chemotherapy or chemoradiation therapy had to have been completed at least six months prior to enrollment. Patients were randomized to receive either FFG-FA 100 mg/m² intravenously over one hour or 5-FU 450 mg/m² as an intravenous bolus after FA therapy, followed by 5-FU 600 mg/m² as a continuous intravenous infusion over 22 hours on days one and two, and 5-FU 400 mg/m² as an intravenous infusion over two hours on day one, FA 200 mg/m² as an intravenous infusion over two hours on days one and two, and 5-FU 400 mg/m² as an intravenous bolus after FA therapy, followed by 5-FU 600 mg/m² as a continuous intravenous infusion over 22 hours on days one and two of a 14-day cycle. Bevacizumab, 5 mg/kg, intravenously was administered as a 90-minute infusion immediately prior to oxaliplatin on day one of each 14-day cycle. Bevacizumab was added to the regimens when the FDA approved for this indication. The primary endpoint of the study was overall response rate (ORR). Secondary endpoints included OS, time to progression (TTP), and adverse events.

Results: Eighty-four patients were enrolled in the study, 42 in each arm. Eighteen in each arm received bevacizumab. Patient characteristics were well-balanced, except there was a higher percentage of patients...
with the colon as the primary site of disease in the FOLFOX4 arm (35 vs. 25), and more patients in the FFG arm had metastatic disease (25 vs. 20). The ORR was higher for the FOLFOX4 arm vs. the FFG arm (40.5% vs. 9.5%; p = 0.002). The results for TTP and OS did not differ between the two groups. As expected, peripheral neuropathy was more prevalent in the oxaliplatin-treated patients (42.9% vs. 2.4%; p < 0.001).

**Conclusion:** Gemcitabine as a biomodulator of 5-FU in aCRC cannot be recommended at this time. The regimen remains investigational.

**Managed Care Implications:** Additional drugs or new combinations are needed to improve the OS in patients with aCRC. At the present time, gemcitabine has no clear-cut advantage in this patient population.
control rate was defined as complete response (CR) combined with partial response (PR) and stable disease (SD).

Results: A total of 46 patients were enrolled, of whom 17 received capecitabine and 29 were treated with capecitabine-bevacizumab. Patient age was similar in both groups, although more female patients were treated with capecitabine and the colon was the primary site of disease with more patients treated with this combination. The median number of cycles received was nine for capecitabine and eight for capecitabine-bevacizumab. No CRs were noted. There was a higher PR rate in the patients treated with capecitabine-bevacizumab (34.5% vs. 29.4%), but this was not statistically significant. Tumor control rates were also higher with capecitabine-bevacizumab (75.9% vs. 70.6%), but again did not reach statistical significance. The median PFS was 12.8 months for those patients treated with capecitabine-bevacizumab and 11.4 months for those treated with capecitabine (p = NS). Following second-line therapy in nearly half the patients, the median OS was 24 months in the capecitabine-bevacizumab group and 15 months in the capecitabine arm (p = 0.53). Severe gastrointestinal toxicity and thromboembolic events were rare and never fatal.

Conclusion: Both regimens, capecitabine and capecitabine-bevacizumab, are well-tolerated and offer effective tumor control in the outpatient setting.

Managed Care Implications: Capecitabine or capecitabine-bevacizumab may offer an easier outpatient therapy to a selected group of patients with mCRC. Larger studies will need to be done to test the efficacy of this combination vs. other well-established combinations, such as FOLFOX and FOLFIRI with or without bevacizumab.

Title: Long-term effect of aspirin on colorectal cancer incidence and mortality: 20-year follow-up of five randomized trials.

Authors: Rothwell PM, Wilson M, Elwin C-E, et al.


Purpose: Colon cancer is the second most common malignancy in developed countries, with a lifetime risk of 5% and approximately 1 million new cases a year and 600,000 deaths worldwide. Most colorectal cancers develop from adenomas, and trials have shown that aspirin or cyclo-oxygenase-2 (COX-2) inhibitors reduce the recurrence by 20%. However, after a mean follow-up of two to three years, these trials were unable to establish any effect on colorectal cancer. Given the delay from early development of an adenoma to presentation with colorectal cancer, follow-up may have been insufficient. This trial did a longer term follow-up of three large trials of daily low-dose aspirin, 75 to 300 mg, in prevention of vascular events. These data were pooled with previously reported long-term follow-up of two additional trials of high-dose aspirin. The goal was to establish the effects of aspirin on the incidence and mortality due to colorectal cancer in relation to the dose and duration of trial treatment.

Methods: Trials of aspirin vs. control in the U.K. or Sweden in the 1980s and early 1990s were studied because these countries had centralized death certification established by this time, making these data available for research. Eligible trials had to recruit at least 1,000 participants and had to have a median scheduled treatment period of at least 2.5 years, because the effect of aspirin on risk of colorectal cancer increased with treatment duration at high doses. Five trials met these criteria. Four of the trials – Thrombosis Prevention Trial (TPT), Swedish Aspirin Low-Dose Trial (SALT), UK-TIA Aspirin Trial, and British Doctors’ Aspirin Trial (BDAT) – compared aspirin vs. control. The fifth trial, the Dutch TIA Aspirin Trial, looked at different doses of aspirin in treatment groups.

Results: A total of 14,033 patients were randomly assigned between aspirin and control in the TPT, SALT, UK-TIA, and BDAT. Duration of follow-up was 17 to 20 years in
TPT, 18 to 23 years in SALT, 21 to 27 years in UK-TIA, and 22 to 23 years in BDAT. Follow-up was 17 years in the Dutch TIA trial. In the four aspirin vs. control trials, the mean duration of treatment was six years. A total of 391 patients, or 2.8%, developed colon cancer during a median follow-up period of 18.3 years. Allocation to aspirin reduced the 20-year risk of colon cancer (incidence hazard ratio [HR] 0.76, 0.60 to 0.96, p = 0.02; mortality HR 0.65, 0.48 to 0.88, p = 0.005) but not rectal cancer. Where data was available, aspirin reduced the incidence of cancer in the proximal colon (HR 0.45, 0.28 to 0.74, p = 0.001) but not the distal colon. Duration of use was also a critical factor for reduced risk, particularly in the proximal colon. Those patients treated for five years or more with continuous aspirin therapy were shown to have a 70% reduced risk of developing cancer (HR 0.35, 0.20 to 0.63, p < 0.0001). There was also a reduced risk of rectal cancer in the same population (HR 0.58, 0.36 to 0.92, p = 0.01). There was no increase in benefit from aspirin dosage of more than 75 mg per day with an absolute reduction of 1.76% in 20-year risk of any fatal colorectal cancer after five-year scheduled treatment with 75 to 300 mg daily. In the Dutch TIA trial, the risk of fatal colorectal cancer was higher on a 30 mg daily dose of aspirin vs. a 283 mg daily dose (odds ratio 2.02, 0.70 to 6.05, p = 0.15).

**Conclusion:** Aspirin taken for several years at a dose of at least 75 mg daily reduced the long-term incidence and mortality due to colorectal cancer. Benefit was greatest for cancers of the proximal colon, which are not prevented effectively by screening methods currently available.

**Managed Care Implications:** Daily low-dose aspirin may become a standard to lower the incidence of colorectal cancer in the appropriate patient population. Since this was not the primary endpoint of any of the trials and adverse reactions were not reported, additional studies may need to be done to assess the risks of this type of long-term aspirin therapy.

**Title:** Adjuvant mFOLFOX6 with or without cetuximab (Cmab) in KRAS WT patients with resected stage III colon cancer: results from NCCTG [North Central Cancer Treatment Group] intergroup phase 3 trial N0147.

**Authors:** Alberts SR, Sargent DJ, Smyrk TC, et al.

**Reference:** J Clin Oncol. 2010;28:18s (suppl; abstract CRA3507).

**Purpose:** FOLFOX (fluorouracil, leucovorin, and oxaliplatin) is the standard adjuvant therapy for stage III colon cancer. Adding cetuximab (Erbitux) to FOLFOX benefits patients with mCRC who are KRAS WT. This study evaluates the addition of cetuximab to FOLFOX in this patient population.

**Methods:** Following resection and KRAS determination, patients were randomized. Patients who were KRAS WT (+) were randomized to receive oxaliplatin 85 mg/m² intravenously on day one with leucovorin 400 mg/m² intravenously, 5-FU 400 mg/m² intravenously by bolus, followed by a 46-hour intravenous infusion of 5-FU at a dose of 2,400 mg/m² (mFOLFOX6). In addition, arm D received cetuximab and arm A did not. The dose of cetuximab was 400 mg/m² intravenously cycle one,
day one only, followed by 250 mg/m² intravenously weekly. Cycles were repeated biweekly for 12 total cycles. The primary endpoint was three-year disease-free survival (DFS). Secondary endpoints included OS and toxicity.

**Results:** A total of 1,760 patients – arm A, 858, and arm D, 902 – were enrolled in the trial. A median follow-up of 15.9 months on 1,624 patients was established. Three-year DFS favored those patients treated with mFOLFOX6 alone – 74.1% vs. 73.3% (HR 1.18, 95% CI 0.92 to 1.52; p = 0.33). There was no benefit of cetuximab noted in any subgroup assessment. Three-year OS also favored the mFOLFOX6 alone arm – 87.3% vs. 82.1%; p = 0.06. In regards to adverse events, grade ≥ 3 diarrhea (8.0% vs. 14.5%; p < 0.001) was much more prevalent in arm D. The percentage of patients able to complete 12 cycles of chemotherapy was higher in arm A (77.3% vs. 65.5%; p < 0.001), secondary to the adverse reactions noted in arm D.

**Conclusion:** The addition of cetuximab to mFOLFOX6 in this randomized phase 3 trial showed no benefit for patients with resected stage III KRAS WT colon cancer.

**Managed Care Implications:** The benefit of the addition of cetuximab to a FOLFOX regimen has been seen only in patients who are KRAS WT (+) with metastatic disease. Adjuvant use of the drug in patients with earlier-stage disease is not warranted.

**Title:** A pilot study on the immunogenicity of dendritic cell vaccination during adjuvant oxaliplatin/capecitabine chemotherapy in colon cancer patients.

**Authors:** Lesterhuis WJ, de Vries IJM, Aarnzen EA, et al.


**Purpose:** It has been a commonly held opinion that chemotherapy and immunotherapy should not be combined secondary to the myelosuppressive effects of the cytotoxic agents. However, there is now data to support that chemotherapeutic agents can have several beneficial effects upon the immune system. For example, treatment with gemcitabine results in increased antigen cross-presentation, T-lymphocyte expansion, and T-cell infiltration of tumors. Studies in animal models provide a rationale for the combination of chemotherapy and immunotherapy in colon cancer. In murine models, the combination of a peptide vaccination and 5-FU (Adrucil) resulted in a significant delay in tumor growth as compared with 5-FU or the peptide alone. Platinum-based chemotherapy is the cornerstone of many types of cancer therapy. Other than its direct cytotoxic effects, it may also exert its clinical effect through indirect activation of the immune system via induction of immunogenic tumor cell death. A stimulatory effect of chemotherapy on tumor immunogenicity without impairing immune effector cell function would provide a strong rationale to develop novel immunotherapeutic strategies. For this reason, this study investigated whether an oxaliplatin-based chemotherapy regimen combined with antigen-specific vaccination in cancer patients can result in tumor antigen specific immune reactivity.

**Methods:** This was an open-label, single-institution exploratory study in patients with stage III colon cancer. Patients received adjuvant treatment with monocyte-derived mature dendritic cells (DC) loaded with carcinoembryonic antigen (CEA) peptide in combination with standard oxaliplatin (Eloxatin/capecitabine, Xeloda) chemotherapy. All patients had to be at least 18 years old, have an
ECOG performance status of 0 or 1, and have adjuvant therapy initiated within eight weeks of surgery. Eligible patients also needed to have adequate end-organ function. Exclusion criteria included the use of immunosuppressive drugs. The primary endpoint of the study was to assess the immunogenicity of the vaccine during oxaliplatin/capecitabine chemotherapy. Secondary endpoints were the toxicity and feasibility of CEA-specific vaccination in this patient population during chemotherapy. Patients underwent leukapheresis for collection of peripheral blood mononuclear cells for DC culture prior to the first cycle of chemotherapy. Dendritic cells were harvested at day seven following isolation culture in Cellgro medium enriched with interleukin-4 and granulocyte-macrophage colony stimulating factor. Additional growth factors were added during the harvesting process. DCs were pulsed with the wild type CEA-peptide CAP-1 directly after harvesting or thawing. Patients received eight cycles of oral capecitabine 2,000 mg/m²/d on days one through 14 and oxaliplatin 130 mg/m² intravenously on day one of each cycle, which was 21 days in length. At days four, 10, and 17 of the first cycle of chemotherapy, patients received three vaccinations, both intradermally (5 x 10⁶ cells) and intravenously (10 x 10⁶ cells), of the CEA-peptide loaded DCs. After completion of the vaccinations, a delayed-type hypersensitivity (DTH) skin test was performed on day 19, followed by biopsies of DTH injection sites on day 22. Dexamethasone was not administered as an antiemetic during the first cycle of chemotherapy. Results: A total of seven patients were treated in this study with a median age of 55 years (range 47 to 75). Most experienced grade 1 fever and flulike symptoms following vaccination. One patient had a grade 2 allergic reaction. Other toxicities included nausea, vomiting, and diarrhea, which may have been chemotherapy-related. With a median follow-up of 18 months (range 10 to 35 months), all patients were recurrence-free. In four patients (57%), functional CEA-specific T-cell responses were found at DTH skin testing. An enhanced nonspecific T-cell reactivity upon oxaliplatin administration was observed. T-cell responses remained unaffected by chemotherapy administration, whereas B-cell responses were diminished. Conclusion: These results strongly support testing of the combined use of specific antitumor vaccination with oxaliplatin-based chemotherapy. Managed Care Implications: Although this was a very small, single-institution study, the results suggest that vaccine therapy in combination with oxaliplatin-based therapy in patients with colon cancer may lead to improved results. Only further testing of this type of combination chemo- and immunotherapy will definitively answer this question.
This resource guide features links and websites specific to colon cancer that may be of use to the reader in daily practice.*

**American Cancer Society (ACS).**
The ACS is a national, community-based voluntary health organization that offers programs for education, patient service, advocacy, and rehabilitation. This detailed guide provides information on risk factors, diagnosis, staging, and treatment of colorectal cancer.

**American College of Gastroenterology (ACG).** The ACG sponsors a broad array of activities, services, and membership benefits, as well as activities supporting the interests of physicians in the gastrointestinal health field. This portion of the website provides a link to physician resources.
www.acg.gi.org/physicians

**American Society of Clinical Oncology (ASCO).** This nonprofit organization is committed to improving cancer care and prevention, advancing the education of those caring for cancer patients, and supporting cancer research. This website offers clinical practice guidelines, research, and other resources for treating colorectal cancer.
http://gicancers.asco.org

**Colon Cancer Alliance (CCA).** The CCA is the oldest and largest national patient advocacy organization dedicated to ending the suffering caused by colorectal cancer. The website provides information for patients and family members on staging and treatment, quality-of-life issues, end-of-life concerns, and more.
www.ccalliance.org

**Colorectal Cancer Coalition.** Also known as C3, this national nonprofit advocacy organization provides a voice for patients in Congress and in regulatory agencies. It also works to educate patients and caregivers about the disease. The website details policy issues and research findings regarding colon cancer.
http://fightcolorectalcancer.org

**Emedicine Health.** Owned and operated by WebMD, this consumer health information website contains health and medical articles written by physicians, including a wealth of information regarding colon cancer.
www.emedicinehealth.com/colon_cancer/article_em.htm

**Mayo Clinic.** The largest integrated, not-for-profit group practice in the world, the Mayo Clinic uses its vast physician expertise to provide information and resources to help consumers manage their health. This website section is devoted to issues regarding colon cancer.
www.mayoclinic.com/health/colon-cancer/DS00035

**MedlinePlus.** A service of the U.S. National Library of Medicine and the U.S. National Institutes of Health, this website offers links to peer-reviewed articles and abstracts on colorectal cancer, clinical trial information, glossaries, statistics, and much more.

**National Cancer Institute (NCI) – Colon and Rectal Cancer.** The NCI, part of the U.S. National Institutes of Health, conducts and supports cancer-related research, training, and health information dissemination. This online guide provides patient information plus links to published literature and research on colon cancer.
www.cancer.gov/cancertopics/types/colon-and-rectal

**National Center for Biotechnology Information (NCBI).** The NCBI is a national resource for molecular biology information, providing access to biomedical and genomic information. The organization’s mission is to develop new information technologies to aid in the understanding of fundamental molecular and genetic processes that control health and disease.

**National Comprehensive Cancer Network (NCCN).** The NCCN strives to improve the quality, effectiveness, and efficiency of oncology care. It publishes clinical practice guidelines that are developed through an evidence-based process, including the current practice guidelines for colon cancer. Users must register to access guidelines.
www.nccn.org/professionals/physician_gls/f_guidelines.asp

**U.S. Food and Drug Administration (FDA).** The FDA is conducting a project to evaluate potential endpoints for cancer drug approval for colorectal and other common cancers. Guidance documents regarding current conclusions of these endpoints will be published.

*Note: ICORE Healthcare does not endorse or verify the information presented.*
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